

Turning of the Tide?

FROM all appearances, it seems as if the United States has once more begun to regard scientific activities as valuable investments of public funds. The Administration's budget, published last week, has done a lot to make good the follies of a year ago, when the Administration failed to appreciate that the Mansfield Amendment restricting the freedom of the Defense Department to sponsor basic research would be seriously damaging if not accompanied by arrangements for keeping good projects going, and when this elementary lack of foresight was coupled with unnecessary meanness towards the National Science Foundation. In particular, it will be good to know that institutions such as the Magnet Laboratory at the Massachusetts Institute of Technology will now be kept alive under the umbrella of the National Science Foundation, that the radio telescope at Arecibo in Puerto Rico will be resurfaced after all and that there is to be no interruption of work on the Cerro Tololo Observatory in Chile. The fact that the extra amount of money to be spent on individual grants at the universities with active research programmes will amount to only \$25 million—about 10 per cent of what is spent at present—may at first sight be a disappointment. Yet, after the deprivations of the past few years, it should be enough to provide a valuable impetus to what the universities are at present doing. In the long run, especially if this year's increase can be regarded as a harbinger of things to come, it will also help to restore morale and give universities in the United States once more the illusion, perhaps even the conviction, that they have a useful role to play in national life.

A loosening of the purse strings for basic research will not, however, obscure the difficulties which persist about the organization of the support for fundamental research in the United States. Although the National Science Foundation (if Congress approves) will for the first time enjoy a budget exceeding \$600 million, its expenditure on scientific research as such will remain a small part—just over 18 per cent—of Federal expenditure on long term research. The new proposal has helped to redress the balance—in the current financial year, 16 per cent of research at colleges and universities comes from the NSF—but there is a long way to go to the point at which the National Science Foundation is responsible, as it should be, for about half of all Federal expenditure on basic research. The awkward consequences of the present arrangements are plainly to be seen even in the new and somewhat encouraging budget. The Atomic Energy Commission, for example, apparently unscathed by rumours about its future in the past few months, will continue to spend the bulk of all the money that finds its way into research in high energy and nuclear physics. In 1972, for example, high energy physics will take \$114 million, substantially the amount which has been spent on work like this in the past few years.

The difficulty, of course, is that in the United States there is no mechanism comparable with that in Britain and elsewhere by means of which these comparatively very large amounts of money can be weighed against the much more modest sums devoted to oceanography, meteorology and the like. In present circumstances, there may

be a case for continuing to invest in high energy physics, but it is absurd that this decision should be taken not by the National Science Foundation, the agency best qualified to assess how the pattern of research expenditure should develop, but by a tug of war between the Atomic Energy Commission and the Administration personified by the Office of Science and Technology. In exactly the same way, it is hard to appreciate why the National Institutes of Health should continue to be such powerful arbiters of the pattern of university research—in the coming financial year, the National Institutes of Health will be responsible for nearly 45 per cent of all the Federal money spent on research and development in academic institutions—an increase from this year to next. Is there not a powerful case for asking that the Administration should concentrate its activities in the support of basic research?

The black spot in the budget of the NSF is the lack of any change of policy on the training of research students. Last year, one of the more tactless provisions of the budget was that training grants for postgraduate students should be dropped. There is no sign that the Administration has budged an inch from this point of view. The consequence is, of course, not so much that doctoral students have disappeared from American universities—quite often they turn up disguised as research assistants carried as overheads on grant applications—but that the Administration has thrown away one means by which it could seek to distribute its funds according to criteria different from those used in awarding research grants. In particular, the studentships were once regarded as a method of helping less well established universities to climb up the pecking order. It may be true, as some cynics have it, that a government's best way of controlling the demand for expenditure on science and technology in the years ahead is to restrict the numbers of graduate students and graduate schools, but this is a counsel of despair which brings nobody credit. In this sense, the passivity of the National Science Foundation in its apparent willingness to disperse research funds without regard to the identity of the institution at which they will be spent, and in particular its willingness to go along with the old doctrine that the inherent virtues of an application for funds should override questions such as the desirability of concentrating work in one field at a few centres, is one of the foundation's most old-fashioned and endearing traits.

If the National Science Foundation and its pensioners will be made more cheerful by the new budget, even the most vulnerable of what are called the mission oriented agencies need not be too downcast. In spite of fears that the National Aeronautics and Space Administration would finish up as an emasculated poor cousin of the US Air Force, the Bureau of the Budget has not been nearly as beastly as it might have been. In the year ahead, the agency will spend some \$3,270 million, a reduction of a mere 0.8 per cent. Moreover, the agency's saving on the exploration of the Moon—\$300 million altogether—will be more than offset by increases of expenditure on the space-shuttle—one of the agency's least happy notions—and the "skylab" to be put in orbit about the Earth later in the decade. It remains a serious weakness in the latter



of the agency's activities that such a very large sum of money should be spent on a single aspect of space research and development, particularly when it now seems clear that the Defense Department will also increase its activity in this field. On the face of things, there is the strongest possible case for asking that the agency should spread its energies (and its money) more widely in the support of more demonstrably useful or interesting projects than the shuttle and the Grand Tour by means of which a rocket will be sent towards the outer planets. Here again the problem is neither a lack of money nor lack of good intentions but a lack of intelligent direction. When will the Administration decide who is to manage NASA in the years ahead?

The fashion for concern about the environment seems

now to be reflected accurately in the budget. In the year ahead, the Federal Government reckons to spend \$2,014 million on all kinds of activities, but more than half the total consists of financial assistance for local authorities which have promised to improve their methods of dealing with sewage and other polluted water. In other words, the core of the Administration's programme for environmental improvement remains what it has been for the best part of a year—Mr Nixon's promise to spend \$5,000 million on a programme to encourage local authorities by means of matching funds to set their own frequently noxious houses in order. Since then, of course, there has been all kinds of evidence to suggest that this sum of money will hardly scratch the surface of what will be needed if rivers in the United States are to be thoroughly cleansed.

More Marking Time

IF the National Science Foundation and its partners in the United States seem to have better things to which to look forward, and even a little more to spend in the years immediately ahead, the research councils which play similar parts in Britain have much less cause for cheerfulness. The latest declaration by the British government on government expenditure (see page 364) has even taken away from the research councils some £3 million provisionally allocated for 1972–73. In the current year, it is expected that the research councils will spend £106 million and by 1974–75 expenditure is provisionally expected to increase to £125 million, representing an increase of 17.5 per cent in four years. Between now and next year, there will be a 4.6 per cent increase of expenditure by the research councils, but thereafter it seems that the government now expects the rate of growth to decrease. Over the period of five years covered by the new estimates of public expenditure, it now seems plain that the government has settled for a rate of growth which will most probably be less than that of the gross national product and very much less than the rate of growth that there might be if the British economy were stimulated by membership of the European Economic Community. Whatever the immediate effect of this parsimony may be, the serious issue which the White Paper on public expenditure has implicitly raised is whether it must now be considered wise that for half a decade the money spent on scientific research of a basic character should be a declining percentage of the gross national product.

The most obvious difficulty is of course that there are no absolute criteria for deciding how much it is proper to spend on scientific research. In the xenophobic early sixties, when it emerged that the United States was spending roughly three per cent of its GNP on research and development of all kinds, and when the United Kingdom seemed to be only a short distance behind (and well ahead of everybody else), there seemed good reason to believe that the magic figure of three per cent was a kind of natural constant, a golden mean. Quite properly, the numbers game is now discredited—a nation can always make itself look good in such comparisons either by spending large sums of money on pointless programmes of research and development or by so mismanaging its affairs that the economy as a whole grows slowly. So should the amount of money spent on basic research be linked somehow with the

growth of higher education as a whole or at least with the growth of the university component in higher education? A few years ago, this argument seemed to be capable of providing an objective yardstick to determine the amount of money to be spent on scientific research. The trouble, now apparent, is that even academics seem willing to acknowledge that the expansion of higher education now necessary in Britain can only be accomplished by qualitative changes in the pattern of academic life and in particular by what may seem to be a dilution of research activity in universities. To be sure, universities as a whole have not yet faced up to the implications of all the changes that the expansion of higher education will make necessary. Certainly there is a long way to go before they will agree that skill in teaching should be counted as an equal with competence in research in determining the esteem in which an academic is held by his colleagues (and the speed with which he is promoted). But the process is under way. Time will bring several changes.

So what is the ditch in which those with the interests of basic research at heart should make their last stand? One possibility would be to insist that there should be no actual decrease in the amount of intellectual energy devoted to scientific research in countries such as Britain but this, of course, is too simple a rule. Most probably, for example, high energy physics is still too well favoured in the British budget for scientific research, at least by the standards to which other disciplines are accustomed, so that adjustments within the science budget could free resources to support neglected fields. And, of course, there are many who argue that the amount of scientific research being carried out in Britain is in any case too great, not merely because much of the work which the universities carry out is subsequently neglected by industry but also because, at least at present, those who have been trained as scientists at the universities are often hard pressed to find employment afterwards. Even these, however, are insubstantial arguments and it should in any case be recognized by the critics outside that, at the present rate of growth of the science budget in Britain, the universities will be unable to keep pace with what is called sophistication—the inexorable increase in the real cost of employing an individual in research which is occasioned by the increasing refinement of the methods and objectives of scientific research. In reality, however, the definition of the last ditch cannot be numerical but

must be qualitative. It is possible to argue, for example, that in spite of over-investment in high energy physics in the recent past it would now be folly for the British government to contract out of the business altogether. To begin with, there is important work in progress. Several university departments have been fashioned round the subject, while the intellectual investment in the operations of CERN at Geneva is too great to be dismissed.

A decision to change course on issues like this would leave scars on British scientific life that would almost certainly be permanent. By the same test, with all the efforts spent in the late sixties on the encouragement of astronomy, it would now be foolish to neglect the opportunities that have been created and also absurd to invite the people concerned to make their homes elsewhere. But the same things can be said of British work

in molecular biology, genetics, and a host of other fields. It is also clear that there is a need deliberately to encourage scientific research when there are industries crying out for technical support of one kind or another. In short, there are perfectly tangible if qualitative reasons why there should be a deliberate attempt to encourage scientific research of particular kinds in the long term. The government, fair play, is sufficiently preoccupied with principles of good management to sponsor all kinds of reviews of the machinery used for the administration of scientific research, but what really needs to be accomplished, not necessarily by the government as such, is a comprehensive review of those parts of scientific research which cannot be neglected in the years ahead. Until that is carried out, there will be no way of demonstrating that the present intention to allow basic research for practical purposes to decline is mistaken.

Living and Partly Living

THE Architectural Association, the independent school for the training of professional architects to which a great deal of the British architectural profession owes its allegiance and even existence, is now more than ever in hazard. Two weeks ago, its second appeal to the Inner London Education Authority for recognition (and support) as a college of higher education was turned down. Evidently the authority considers that it already spends enough on educating architects, and there is much in that. In retrospect, it must be galling to all concerned to recognize that it might by now have been possible for the Architectural Association to have forged some link with London if it had not chosen, instead, to waste several years on negotiations with Imperial College which eventually proved abortive. Although it is not clear why the attempt to make the Architectural Association into an institute of Imperial College failed, especially because it seems even in retrospect that the architects and the engineers would have had a lot to say to each other, the chances are high that the association's experience then will be repeated in any future attempt to marry with an established university. At least one stumbling block is constitutional—the Architectural Association is governed (if that is the word) as much by the students as the faculty, but it is also a big mouthful for any university to swallow: 400 students in architecture could not be accommodated anywhere without disturbance.

So what is there left to do? In the past few days, the Architectural Association has been heartened to be told by its students that they at least would like to soldier on. Their view appears to be that the advantages of the distinctive education provided at the Architectural Association are so great that the risk eventually of seeing the institution shut down before their courses are complete is something to be lived with. The result is that, by all accounts, the association is now again proposing to tackle its friends to see whether it would be possible to raise a sum of money large enough to keep the familiar wolf from the door. In a funny way, and from sheer necessity, the association is trying to solve all the problems that confront or will confront the independent university if that should ever become more of a reality than it is at present. As such, the example in the next few months should be an important object lesson for lots of people. The association's problem

is that it has no direct support either from the University Grants Committee, which keeps the universities in being, or from a local authority as might a polytechnic. The result is that the real cost of teaching must be met either by fees or endowment income. The Architectural Association reckons itself to be a good housekeeper by its capacity to run its affairs for £600 per student per year, although the facilities which it offers for that would frequently provoke revolutions at other institutions. The fees charged to students are £460 a year, much larger than the nominal sums asked of students at universities and polytechnics, with the result that many local authorities are frequently less willing than they should be to help their students through courses at the Architectural Association. Even so, roughly three-quarters of the students are supported in this way. Evidently the margin between success and failure is comparatively narrow. At a time when most teachers complain of the apathy of their students, it would be a great misfortune if one of the places which they appear to relish should close down for want of benefaction.

100 Years Ago



THE *Scientific American* states that the Board of Trade of the city of Buffalo has obtained a franchise and organised a company to be styled the Oxyhydrogen Gas Company, having for its object the introduction of the oxyhydrogen gas light into that city. A committee of investigation has visited the oxygen gas works in New York, and with the information thus obtained we are informed that the work is to proceed at once. It would appear that Buffalo is to be the first city in America to adopt this splendid light. The experiment is an important one, and its success will be watched with considerable interest by gas consumers in this country and America.

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OLD WORLD

SELECT COMMITTEE

No Space Policy

SUBCOMMITTEE B of the Select Committee on Science and Technology discovered this week that the Ministry of Aviation Supply has less than complete control over the development of Britain's policy for space research. Although that suspicion may have already been in their minds, members of the subcommittee were left in little doubt of its reality when they took evidence from Mr E. C. Cornford, Controller, guided weapons, Mr A. Goodson, Head of the Space Division, and Mr J. Lewis, of the R & D branch at the Ministry of Aviation Supply, during the first public meeting this session.

The witnesses told the committee that the Ministry of Aviation Supply plays a central, technical role in Britain's space activities, in that its chief function is to provide the space technology required by other departments for their own space purposes. The Ministry of Defence is, however, responsible for military communications satellites, the Department of Education and Science for scientific space research, and the Ministry of Posts and Telecommunications develops policies for civil communications by satellite. No amount of questioning by members of the select committee could bring out evidence to suggest that the programme which results from the deliberations of these various ministries has any real community of purpose, and Mr Goodson was even forced to admit that "there is no space programme which stands on its own merits".

The Ministry of Aviation Supply is, however, responsible for the development

of Britain's policies for international co-operation in space research, and this was subject to extensive probing by members of the subcommittee. Mr Richard Brown, in particular, wanted to know whether the fact that expenditure on international space activities is now only about half that on national space research represents a change in policy—four years ago, the bias was the other way round (see Table 1). But Mr Goodson explained that the chief reason for the decrease in international research expenditure is that the British government decided in 1968 to leave ELDO, while much of the increased expenditure on the national space programme has been devoted to the development of the Skynet military communications satellite.

Mr Brown pointed out that one of the chief reasons why ELDO never developed into a viable organization is that many countries used the development of the Europa launcher as a means of getting some economic return for their obsolete defence rockets. He also believed that because ELDO is chiefly a procurement agency, which does not have much say in the development of satellites, its launchers are not necessarily the best ones for launching European satellites. He wondered whether the Ministry of Aviation Supply has got itself into a similar position with respect to the British space programme, in that it may be developing a launcher which nobody will want. But Mr Cornford did not agree. He said that Black Arrow is a small, cheap and simple satellite launcher which is tailored to the experimental programme that it is meant to serve. Development of the Black Arrow Launcher is solely the responsibility of the Ministry of Aviation Supply, but the Department of Education and Science will formulate its own policy for

the experimental satellites that it may launch.

In their written evidence to the select committee, the witnesses confirmed that a launch attempt will be made later this year with the X3 satellite, carrying technological experiments (see *Nature*, 229, 290, 1971), but that the Black Arrow launch which was scheduled for December 1971 had been put off because of difficulties with satellite development. The satellite was to contain two meteorological experiments and an attitude control experiment, and was intended to be a joint project between the Ministry of Aviation Supply and the Meteorological Office. In December 1970, however, the Meteorological Office backed out of the project, and it is now being reviewed.

HIGH ENERGY PHYSICS

Nina Shines

THE Science Research Council is putting up £360,000 to exploit the synchrotron radiation that is generated by electrons in the Nina electron accelerator of the Daresbury Nuclear Physics Laboratory, near Manchester. This was announced on Tuesday and work has already begun at Daresbury on the new laboratory which is expected to be ready by mid-1972. At first, at least, it will have its greatest application in solid state physics.

Funds for the synchrotron radiation facility come under the Science Board of the Science Research Council rather than the Nuclear Physics Board which is responsible for the Daresbury laboratory and which must be hard pressed just now finding ways of pruning its requirements to make entry into the 300 GeV project easier. Rather the new facility is an instrument that chemists, biologists, and physicists outside nuclear physics will want to use, and it has the charm that they can be using the intense synchrotron radiation from the accelerator while the nuclear physicists are working unimpeded with the 5 GeV electron beam.

Up to now the synchrotron radiation that is emitted by electrons in circular paths (and so called because it was first observed in electron synchrotrons like that at Daresbury) has gone to waste, so to speak, in the Daresbury accelerator. Most of the money that has now been earmarked will go towards building an arrangement for the extraction of the light from the vacuum tube in which the electrons are accelerated without interfering with the beam and the provision of ancillary equipment such as spectrometers. But some of it will be available to finance experiments using the radiation that is made available.

When the new facility is built, it means that the SRC will have at its disposal a source of radiation at X-ray and ultra-violet wavelengths (5 Å to 2000 Å) that is more intense than can be obtained with

Table 1 UK Expenditure on Space Activities

	1966/ 67 (1)	1967/ 68 (1)	£000s 1968/ 69 (1)	1969/ 70 (1)	1970/71 (Esti- mates)
<i>International civil programmes</i>					
ELDO (2)	12,540	8,750	9,640	8,170	1,840
ESRO (3)	3,850	4,500	5,000	5,200	5,450
INTELSAT (4)	800	600	1,040	1,030	1,130
Post/Apollo studies	—	—	—	—	230
	17,190	13,850	15,680	14,400	8,650
<i>National programme</i>					
Defence	3,500	4,000	10,700	5,360	6,730
Commercial satellite communications (Post Office Earth Terminals)	1,070	1,170	1,340	1,300	1,600
Scientific space research	2,230	1,960	2,350	2,930	3,930
Space technology and other expenditure not included above	2,770	3,170	4,110	3,830	4,640
	9,570	10,300	18,500	13,420	16,900
Total space	26,760	24,150	34,180	27,820	25,550

(1) Figures for these years represent actual expenditure.

(2) Contribution to the organization (limited to £11 million as from January 1, 1969).

(3) Includes £100,000 for applications studies in 1969/70 and a total of £400,000 in 1970/71 for applications studies, applied research and applications satellites (communications and aeronautical).

(4) INTELSAT figures are the United Kingdom quota payments to the Organization less United Kingdom revenue receipts from the Organization.

conventional sources. The peak of the spectrum will be at a few Ångström, but the immediate interest is expected to be in ultraviolet wavelengths of a few hundred Ångström, which will be a few orders of magnitude less intense than radiation at the peak but nevertheless better than conventional sources. Spectrometers and other equipment will be provided for this wavelength range in the first instance. Another valuable feature is that the synchrotron radiation is emitted in a narrow cone less than a milliradian across.

A panel will be appointed to allot time on the synchrotron radiation facility, which will be available to the universities and other research laboratories. The Science Research Council says it expects the laboratory to be used for such pursuits as the study of inner electrons in atoms, X-ray crystallography, and examination of biological specimens.

FOWL PEST

Outlook Gloomy

ALTHOUGH the daily tally of fresh outbreaks of fowl pest has shown a slight downward trend recently, there seems little in store to cheer Britain's poultry farmers. An expert in Newcastle disease predicted last week that although use of the Hitchener B1 live vaccine is already showing beneficial effects, it could well be two years before the disease is cut back to something approaching the pre-epidemic level.

By January 31, 1971, more than 4,500 cases of fowl pest had been reported from 51 counties. Late last year there were signs that the disease had run its course, but these have proved false omens; the direction of the wind changed, and the disease was carried from East Anglia to set up fresh centres of infection in Derbyshire and elsewhere. The virus causing the epidemic has already become known as "Essex 70"—a grudging tribute to its virulence and obstinacy.

What should have been done when the outbreaks started is now only of historical interest. The breeders claim that an immediate slaughter and compensation operation should have been mounted, whereas the Ministry of Agriculture has laid the blame squarely on those breeders who failed to maintain full and adequate protection in their stock. What is important are the steps now being taken to contain the epidemic and to prevent the recurrence of a similar tragedy. Both the Ministry and the National Farmers Union agree that more information must be made available to breeders about vaccines and vaccination. The Hitchener B1 vaccine is already in use, and trials are under way with the La Sota live vaccine, but Mr Wellstead, Secretary of the Poultry Committee of the National Farmers Union, pointed out that the use

of these live vaccines is nowhere near so simple in practice as it seems in theory. In fact, deciding when and how to apply the vaccine requires great judgment, for there is a complex interplay between the fowl's brief inherited immunity and the need for extra protection.

The only hope of reducing the incidence of outbreaks in the short term seems to lie in vaccination and in greater attention to hygiene. An agricultural scientist said last week that breeders pay too little attention to the arduous task of decontaminating buildings where infected birds have been housed, before moving in fresh, healthy stock. Neither vaccination nor hygienic practices can be forced on unwilling poultrymen by legislation; but perhaps effective propaganda will help to avert similar disasters in the future.

Miscellaneous

NOBODY knows whether railwaymen at Heysham are reading their way through 1,500 copies of *Nature* for January 22, blacked on their way to Dublin in an abortive attempt to beat the postal strike: if so, perhaps the railwaymen are already themselves considering the advantages of dismembering the nationalized industries along the lines recommended for the Post Office (see *Nature*, 229, 218; 1971).

MR RICHMOND POSTGATE, Controller of Educational Broadcasting at the BBC, has contributed to the *BBC Handbook 1971* the memorable claim that "broadcasting is the most penetrating agency of communication, reaching deeper into more homes than any other". What Mr Postgate means is that the claims of the BBC to be an educational agency should not be sniffed at. Somebody should measure the relative depths of penetration of *Guns*, *Smoke* and *New Ways in Thermodynamics*.

ON the principle that to them that hath shall be given, it seems now to be assumed that J. B. Gurdon, distinguished for his embryological work and in particular cloning toads, will move to the MRC Laboratory of Molecular Biology at Cambridge later in the year. Has Oxford used up so much of its seductiveness in attracting molecular biologists from outside that it cannot manage to keep its own?

SOME of the officers of the British Association seem to be hoping that they can solve their chronic problem of what is called illiquidity by merging either with the Royal Society of Arts or with the Royal Institution. Even supposing that such a scheme is feasible, only lawyers can relish the proceedings that would have to be taken to persuade the Privy Council and the Charity Commissioners that such a course would be desirable. The British Association's friends will wonder whether it can last that long.

Parliament in Britain

US Defence Research Contracts

THE United States Department of Defense is financing 69 research projects at 25 universities in the UK. The values of these contracts in 1968, 1969 and 1970 were £324,000, £344,000 and £266,000 respectively, and they were for projects chiefly in the physical sciences. This information was given by Mr Nicholas Ridley, Undersecretary of State, Department of Trade and Industry, in reply to a question from Mr Tam Dalyell. But Mr Ridley said that none of these research projects is classified. In any case, the Department of Trade and Industry has no responsibility for the placing or financial control of the contracts and only receives information on them so that duplication with other government-sponsored research at British universities is avoided. (Written answers, January 25.)

Expenditure on Research

MRS MARGARET THATCHER, Secretary of State for Education and Science, said that government expenditure on research and development in 1970-71 is estimated to be £350 million for civil projects and £230 million for defence. The corresponding expenditures for 1969-70 were £350 million and £233 million. In 1967-68, a total of £962 million was spent in the United Kingdom on research and development, £493 million of which was provided by central and local government, and £405 by industry. This information was given in reply to a question from Mr John Osborn. (Written answers, January 26.)

Channel Tunnel

MR JOHN PEYTON, Minister for Transport Industries, said that the government has now reached the stage of embarking on the final studies of proposals for a tunnel underneath the Channel. Both the British and the French governments have studied the proposals put forward by a private international firm last July, and will soon be discussing with the group how an early start can be made on further studies which must precede the final decision. But Mr Robert Sheldon pointed out that the White Paper on the Channel tunnel is now eight years out of date, and accused the Department of Trade and Industry of not releasing information on traffic studies. He asked for another White Paper to be prepared setting out the objectives of the scheme, and for a revision of the whole concept of the tunnel link. Mr Peyton replied that he is sure that a White Paper will be necessary soon. Mr A. P. Costain also pointed out that the delay in coming to a decision on the project is causing serious inconvenience in the Folkestone and Hythe area. (Oral answers, January 27.)

Cuts in Public Expenditure hit Civil Research

A DECLINING rate of growth in the expenditure of the research councils is outlined in the government's latest declaration of intent to reduce public expenditure. The White Paper published last week (*Public Expenditure 1969-70 to 1974-75*, HMSO, 9s) provides the details of the government's policy for reducing the rate of growth in public expenditure to something less than that of the gross national product, and it is no surprise that the chief casualty of this policy is the Department of Trade and Industry, whose expenditure is being reduced from about £800 million in 1969-70 to about £250 million in 1974-75. The White Paper puts the flesh on the bones of the Chancellor of the Exchequer's announcements last October (see *Nature*, 228, 400; 1970), when Mr Barber said that the government would reduce public expenditure to pave the way for cuts in taxation.

The expenditure of the research councils, including that on agricultural research in Scotland, is expected to be about £110 million in the present financial year, increasing to £129 million in 1974-75. Although this represents an increase of about 27 per cent over five years, the ominous sign is that the annual rate of growth will be decreased from about 4.6 per cent between the current year and the next, to about 4.3 per cent for the next two years, and that it will finally drop to about 3.3 per cent between 1973-74 and 1974-75. The growth in gross national product is expected to reach 3.5 per cent by that time, and the government therefore seems to be planning for a declining proportion of the gross national product to be devoted to civil science.

This decline in the growth rate of the budgets of the research councils will take place chiefly because the government has decided to reduce the expenditure proposed by the Labour Government in its White Paper on Public Expenditure a year ago. The new proposals take £2 million off the proposed budgets of the research councils for next year, rising by £1 million a year to £5 million in 1974-75. A complete review of the expenditure of the research councils is being carried out by the Council for Scientific Policy, and it will look chiefly at how the research councils can involve themselves in more industrial research.

Until the review has been completed, the budgets of individual research councils are likely to remain unclear. The White Paper does, however, give details of the budgets up to 1971-72 (see Table 1). In the newer and more fashionable areas of research—those covered by the Natural Environment Research Council and the Social Science Research Council—expenditure will be increased by more than

the average. The Agricultural Research Council and the Medical Research Council, however, will have to be content with an increase in their funds of only about 3.5 per cent, while the Science Research Council fares worst of all with an increase of 2.6 per cent. These rates of growth can be compared with the overall increase of about 8.5 per cent in the budgets of the research councils this year, compared with 1969-70.

In spite of their comparatively generous increases of 5 per cent and 16 per cent respectively, the Natural Environment Research Council and the Social Science Research Council are far from happy. The SSRC, for example, has had its growth rate cut from 43 per cent last year to 16 next, and this seems to have caused considerable heart searching in the council. It has already announced that two-year awards, both for present and new holders, may be extended only for periods of up to three months. Normally, such awards could be extended for a further year if necessary.

While the White Paper therefore seems to have little to offer to the scientific community, there is a small crumb of comfort in the proposed expenditure on education. Recurrent expenditure on the universities is expected to increase from about £264 million in the current year to about £355 million in 1974-75—a growth of 34 per cent during the next four years. Expenditure on further education, on the other hand, is projected to increase by only 9 per cent over the same period and that on teacher training by 13 per cent (see Table 2). Compared with a projected increase in the numbers of students in full-time higher education—about 25 per cent over the same period—the increase in expenditure on the universities seems to be sufficient to keep pace with student numbers. But, in the face of the government's implied intention to incorporate much of the increase in student numbers in the polytechnics, the planned expenditure on non-university higher education is not so generous.

Table 1 Expenditure by the Research Councils

	1969-70 provisional outturn	£ million 1970-71 estimate	1971-72 allocation
<i>At 1970 Survey prices</i>			
Agricultural Research Council	15.7	16.2	16.8
Medical Research Council	18.5	19.7	20.3
Natural Environment Research Council	12.2	13.9	14.6
Science Research Council	46.4	49.6	51.9
Natural History Museum*	1.2	1.8	1.7
Science: Grants and Services	1.5	1.6	2.2
Documentation Processing Centre	0.2	0.4	—
Social Science Research Council	2.3	3.3	3.8
	98.0	106.5	111.3
* Includes provision for major building			

Table 2 Proposed Expenditure on Education

	1969-70 pro- visional outturn	1970-71 estimate	1971-72 estimate	1972-73 estimate	1973-74 estimate	1974-75 estimate
<i>At 1970 Survey prices</i>						
Capital expenditure:						
Schools	223.5	229.0	274.5	267.3	236	193
Further education	54.3	56.7	59.1	55.2	49	52
Teacher training	8.4	8.3	8.5	6.5	5	4
Universities	75.4	77.5	74.9	77.8	82	92
Total (capital expenditure)	376.2	386.9	434.6	424.9	391	360
Current expenditure:						
Schools						
Primary	461.7	472.3	502.0	523.3	532	536
Secondary	518.1	535.9	571.2	602.2	657	700
Other	133.9	138.0	141.9	146.2	152	158
Further education	249.7	261.2	270.6	283.0	280	286
Teacher training	103.7	108.4	111.1	114.1	118	121
Universities	251.7	263.9	280.8	299.3	323	355
Total (current expenditure)	2,072.4	2,136.1	2,218.6	2,314.8	2,409	2,511
Total	2,448.6	2,523.0	2,653.2	2,739.7	2,800	2,871

NEW WORLD

Keynes and Fancy Footwork avert Science Tumble

by our Washington Correspondent

THE budget for fiscal year 1972, which President Nixon presented to Congress last week, has disappointed the worst fears of the scientific and academic community. Despite recent warnings from science leaders in Washington that federal support of science would at best remain constant, the sums being requested of Congress represent increases of a magnitude that recalls the golden age of science growth in the fifties and early sixties.

The list of increases is one that few would have expected two months ago. Putting the figures in their best light, Dr Edward David, the President's science adviser, was able last week to point to a 15 per cent increase in funds for research and development in colleges and universities (from \$1,653 million in fiscal year 1971 to \$1,896 million in 1972). Total research and development by the Federal Government is budgeted at \$15,555 million, an increase of 8 per cent, and excluding the Department of Defense, NASA and the AEC from this total, research by civilian agencies will rise by 14 per cent to \$8,809 million.

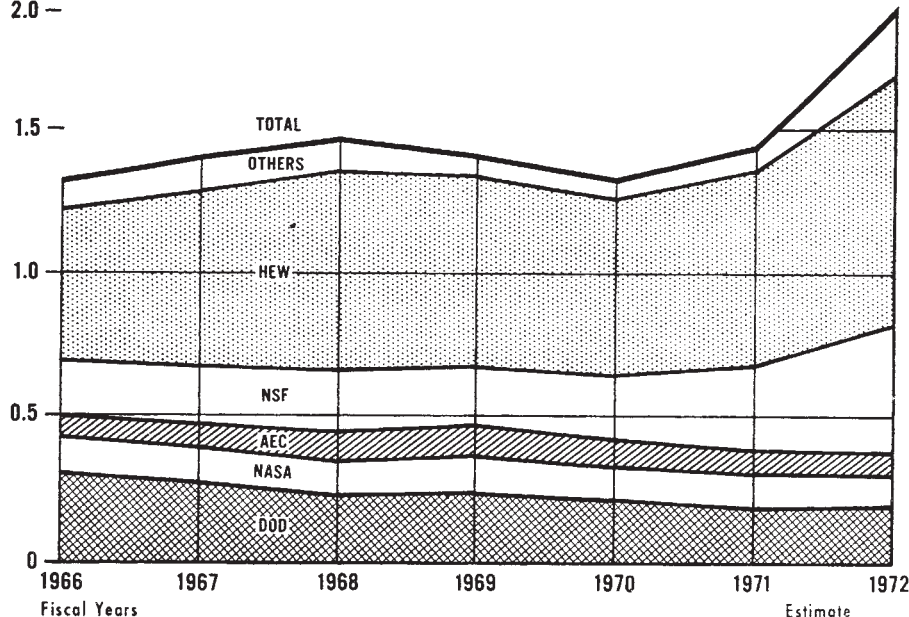
Total obligations being requested for the National Science Foundation are up by 22 per cent, from \$507 million to \$622 million. The National Institutes of Health have picked up an 11.8 per cent increase to \$1,179 million for research and development, and there is an as yet unassigned \$100 million for cancer research.

These sums are, nevertheless, a long way from being money in the bank, since even if Congress appropriates the full amount requested, the actual expenditures in a given year are always less than the full amount obligated (obligations to spend often extend beyond the fiscal year in question). Thus the total funds to be expended by federal agencies in colleges and universities in 1972 are estimated to amount to \$1,678 million, an increase of only 6.5 per cent. Allowing 5 per cent for inflation, it is clear that there will be no very great expansion in academic research during the coming financial year. The budget increase promised for the National Science Foundation is also less than it seems because nearly 75 per cent of the additional \$100 million requested is designed to pick up research activities shed by other agencies rather than to support new ones.

Even if the picture is less bright than at first sight, it is still much better than feared. To whom should scientists address their thanks for the unexpected windfall? It seems that if any one individual deserves the praise, it is Maynard Keynes and the

Obligations for Research in Colleges and Universities

\$ Billions
2.0 —



school of economists which believes in countering unemployment with an expansionist budget. Until the beginning of December last year, Mr Nixon was resolved to follow in the footsteps of previous Republican presidents and balance his budget. The budget review completed in mid-November according to this design in fact contained almost the same dollar amounts for science as were allotted last

year and which because of inflation represent an actual decrease of about 5 per cent.

No wonder that the Office of Science and Technology at this time was warning the scientific community to tighten its belt. In a speech delivered at the Washington Cosmos Club on November 19, for example, Dr Carl York, Technical Assistant for Basic Science at the OST, indicated that, barring another Sputnik-like jolt,

Table 1 National Aeronautics and Space Administration Research and Development

	(In thousands of dollars)		
	1970	1971	1972
MANNED SPACE FLIGHT	2,029,967	1,431,100	1,286,475
Apollo	1,684,367	914,400	612,200
Space flight operations	343,100	515,200	672,775
Advanced missions	2,500	1,500	1,500
SPACE SCIENCE AND APPLICATIONS	519,529	565,700	750,400
Physics and astronomy	112,851	116,000	110,300
Lunar and planetary exploration	150,900	144,900	311,500
Bioscience	19,655	12,900	—
Space applications	128,304	167,000	182,500
Launch vehicle procurement	107,819	124,900	146,100
ADVANCED RESEARCH AND TECHNOLOGY	270,931	264,200	212,825
Aeronautical research and technology	95,685	102,000	110,000
Space research and technology	119,977	107,000	75,105
Nuclear power and propulsion	55,269	55,200	27,720
TRACKING AND DATA ACQUISITION	278,000	290,000	264,000
UNIVERSITY AFFAIRS	7,000	—	—
Sustaining university programme	7,000	—	—
TECHNOLOGY UTILIZATION	5,000	4,000	4,000
TOTAL	3,110,427	2,555,000	2,517,700



Fig. 1 David, Schultz, McElroy and Handler: Making hay while sun shines.

nothing would divert the Nixon Administration from a policy of a balanced budget, in which case, Dr York said, "the physical sciences in the universities must look for essentially no dollar increase and an effective inflationary decrease in their funding".

No Sputnik shattered the skies over the United States in November 1970, but some equally forceful bolt from the blue, conceivably the poor showing of the Republican party in the mid term elections, convinced Mr Nixon that an expansionary budget was necessary to counter the inflation in the economy and reduce unemployment. Early in December, the decision was taken to tear up the balanced budget that had been prepared in favour of one with an \$11,600 million deficit. Several factors seem to have helped deflect a share of the extra money towards the scientific estate, not least the belief of George P. Schultz, director of the Office of Management and Budget, that a healthy scientific research enterprise is good for the economy.

Those inside the government also attribute credit to Foster, David and McElroy (heads of defence research, the Office of Science and Technology and of the National Science Foundation) for their "fancy footwork" in guiding newly available funds towards science and technology. "The rules of the game were changed, and once changed these guys really played beautifully," says one observer. John S. Foster, the Director of Defense Research and Engineering, seems to have done best of anyone, cornering a massive \$900 million increase for military research, but the civilian leaders, David and McElroy, succeeded in winning an additional \$100 million for the National Science Foundation. "Ed David did a great job of orchestrating the availability of these funds and channelling them", says one admirer of the science adviser's contribution.

The policy directions enacted in the budget for science and technology, David said last week, include a determination to maintain and increase United States eminence in basic research, with the National Science Foundation playing

a central role. The NSF is certainly receiving a fatter diet than it was expecting; only in November, Dr William McElroy was complaining in a speech given in Michigan that "scientific research is apparently one of the delicacies that can be trimmed from our national diet". Last week it was a different story: "The National Science Foundation is most conscious," McElroy declared, "of President Nixon's concern for the nation's scientific health."

Despite President Nixon's concern, the extra helping on the NSF's plate does not mean more for the same but simply reflects more mouths to feed. Even if Congress grants the full extra \$100 million being requested of it, \$19 million is earmarked for the ships and facilities used to support Antarctic research, which until now have been operated by the Navy. (The reason for the transfer is to reduce any appearance of military activity in the Antarctic.) Another \$15 million is intended for the support of specific laboratories formerly supported by the Department of Defense—the National Magnet Laboratory and the Interdisciplinary Materials Research laboratories at a dozen universities—a general fund of \$40 million is allocated to salvage some of the physics and engineering projects abandoned by the Atomic Energy Commission, NASA and the Department of Defense.

These prior claims would leave only \$25 million for expanding existing programmes, but much of the new thrust of the foundation's plans for 1972 is aimed at environmental and social research rather than the basic sciences.

In the National Institutes of Health, research funds have remained fairly stationary apart from the extra \$100 million being requested for cancer research. The \$100 million is not included in the budget of the National Cancer Institute and its eventual allocation is to be announced by the President later this month. The National Heart and Lung Institute will receive an extra \$5 million for research on sickle cell anaemia, a disease that affects one in every 400–500 young blacks. Apart from the relatively

small Institute of Dental Research, most other component institutes of the NIH have reductions in their budget or increases insufficient to cover inflation. Excluding the \$100 million for cancer, the total budget of the NIH has risen by less than half a per cent, from \$1,178 million in 1971 to \$1,183 million.

But the Nixon administration has not turned a deaf ear to the cries of the nation's medical schools, expressed most articulately in the recent report of the Carnegie Commission on higher education (see *Nature*, 226, 601; 1970); total federal funds to medical schools will rise from \$866 to \$1,045 million in 1972, an increase of some 23 per cent, in addition to which a special \$95 million programme will be launched specifically to remedy some of the deficiencies cited by the Carnegie Commission.

Both NASA and the Atomic Energy Commission have been even less fortunate than the NIH, although NASA has managed to retain the grand tour of the planets which at one time seemed on the verge of extinction. The total NASA budget has fallen slightly from \$3,369 million to \$3,152 million, but the remaining Apollo flights up to Apollo 17 have been saved. The Skylab space station will fly as planned, though not until after the last Apollo flight, and unmanned planetary probes will continue (see Table 1).

The major emphasis for NASA's future is being staked on the shuttle, for which the 1972 budget includes an extra \$100 million. Research and development for space science and applications shows a substantial increase on 1971, except for bioscience, which has been cut completely. Other categories which have taken cuts are the NERVA nuclear rocket engine, funds for which have been halved, and the university sustaining programme, now axed completely.

The Atomic Energy Commission, the largest supporter of physical research, has suffered major reductions in its support of all categories of physics; the budget for high energy physics alone has dropped by \$12 million to \$114 million, which entails the closing down of the Princeton-Pennsylvania accelerator. Construction

of the 200 BeV machine at Batavia, however, will continue as planned. Other categories of physical research have been reduced by \$12 million to \$259 million.

The vast sums for military research and development included in the budget—a total of \$8,308 million—do not argue any very great confidence in the outcome of the SALT talks, although government officials are at pains to point to other explanations, such as the alleged increase in the Soviet Union's military research spending, the need to mechanize the infantryman as the size of the army is reduced, and the "backlog" of research postponed during the peak years of the Vietnam war. Be this as it may, research efforts on the undersea long-range ballistic system (ULMS) are being doubled and

another \$1,300 million, the same as for fiscal year 1971, is being requested for the Safeguard antiballistic missile system.

At a press conference on November 30 last year, the president of the National Academy of Sciences, Dr Philip Handler, warned that the scientific enterprise was in danger of decaying through lack of financial support and that "science does not have a high priority at this moment" in the Office of Management and Budget. Handler presumably had in mind the level of federal support implied in the balanced version of the budget then prevailing which offered the scientific community the same dollar amounts as for fiscal year 1971. Officials in the Office of Science and Technology, where Handler's independent stand is not alto-

gether appreciated, insist that the Nixon Administration, despite the academic community's persistent disbelief, does have a close concern for academic science and that even in the balanced budget the science agencies would have fared better than others. The abrupt shift in economic policy, and the windfall for science it brought in its train, have to some extent falsified Handler's forebodings as well as causing glee in the Office of Science and Technology at having shown him wrong. Whether or not the new budget will win credit for the Administration among Handler's constituency is another matter, but initial gratitude could turn out to be short lived, especially if Congress should cut the increases below the inflation rate they in some instances barely surpass.

Shopping List for the NSF

by our Washington Correspondent

THE largest single item in the budget of the National Science Foundation is \$257.8 million for individual research projects in all fields and disciplines. It is estimated that some 5,300 individual grants averaging \$48,000 each will be distributed, the beneficiaries being some 7,700 faculty scientists and a nearly equal number of graduate students. Of the increase of \$82 million in this item over last year, some \$40 million will be used by the foundation to pick up fundamental research projects abandoned by other agencies, in addition to which some \$12.8 million has been included for the support of the Interdisciplinary Materials Research Laboratories and \$1.8 million for the National Magnet Laboratory at MIT, both formerly funded by the Department of Defense.

A statement issued by the foundation in explication of its 1972 budget allocations says that "preferential emphasis" in the awarding of this category of grants will be given to "biology of human cells, to broaden our understanding of diseases, genetic damage, and fundamental life processes". Support will be extended to the increasing number of physicists expected to apply to the NSF as the result of cutbacks by NASA, AEC and the Department of Defense. Engineers will find the NSF favourable to projects on super-hard materials and material processing, biomedical materials and the effects of wind on buildings. Chemists should write their grant applications to emphasize "analysis and instrumentation techniques in the areas of molecular processes and configuration, chemical dynamics, and enzymes". In oceanography, ocean dynamics is in, along with currents, salinity and ocean ecology.

The second largest single item in the budget, \$166.6 million for eight national and special research programmes, includes

funds for the support of the international biological programme (\$10 million); the global atmospheric research programme (\$2.5 million), intended to improve long range weather forecasts and to analyse the data gathered during Project Borex; the international decade of ocean exploration (\$20 million), where support will be focused on environmental quality, environmental forecasting and seabed assessment; the ocean sediment coring

the budget for building any of the five new radio telescopes that radio astronomers have been asking for. Optical astronomers stand to receive \$7.7 million for the Kitt Peak observatory and \$2.5 million for the Cerro Tololo Inter-American observatory now under construction in the Chilean Andes. A fifth research centre, the National Center for Atmospheric Research at Boulder, Colorado, has requested funding of \$19 million.

National Science Foundation: Budget Programme Comparisons for fiscal years 1970–1972. (Millions of dollars.) (Amounts shown are obligations, not all of which may be spent in the fiscal year shown.)

Programmes	Actual FY 1970 \$	Estimate FY 1971 \$	Estimate FY 1972 \$
Scientific research and facilities support	168.2	181.7	263.6
National and special research programmes	78.6	117.7	198.9
National research centres	27.2	37.1	40.4
Institutional support for science	44.7	34.5	12.0
Science education support	120.2	100.6	77.3
Programme development and management	21.7	23.7	27.0
Total NSF programmes	440.0	505.9	622.0

programme (\$8.5 million); the arctic research programme (\$3.5 million); research and logistic support of operations in Antarctica (\$26.8 million); oceanographic ships and related facilities (\$14.3 million); and a group of directed research projects aimed at weather modification, earthquake engineering and other goals (\$81 million).

A third major item in the budget is a sum of \$40.2 million intended to support the five national research centres sponsored by the NSF. The radio telescope at Arecibo, Puerto Rico, is down to receive \$4 million nearly half of it for resurfacing the dish. \$7 million is requested for support of the National Radio Astronomy Observatory to continue support of research projects and maintain existing telescopes. There are no funds in

Where the foundation has had to revise its ambitions is in the field of education, apparently because of a decision that science and engineering PhDs are becoming a glut on the market and that there is no need to continue expansion of the system for producing them. Thus the science development programme, which this year is scheduled to provide \$20 million for the improvement of graduate training courses, has been totally extirpated from the 1972 budget request. Postdoctoral fellowships, worth \$2 million in 1971, will exist no more, and graduate fellowships and traineeships are being slashed from \$28.3 million to \$20 million. The overall cut in science education support amounts to nearly 25 per cent, from \$100.6 to \$77.3 million.

NEWS AND VIEWS

Switch Back to Radio Galaxies

DURING recent months, the attention of astronomers has concentrated on curious phenomena in our own galaxy, notably at the high and low ends of the spectrum which can now be studied, and sources ranging from X-ray stars and pulsars to cool clouds emitting microwave radiation have kept cosmology and the study of events outside our galaxy away from the centre of attention. But radio galaxies and other distant objects have remained enigmatic in many ways, and it now seems that some of the knowledge gained from the recent intensive study of high energy sources inside our galaxy can help to explain the behaviour of extragalactic sources. If so, these sources seem certain to become once more the subject of concentrated study by many more astronomers, and another clue to the nature of the universe might be uncovered.

On page 388 of this issue of *Nature*, M. Rowan-Robinson, of Queen Mary College, London, presents the results of a study which shows conclusively that evolutionary effects are significantly large in radio galaxies. This work is more a filling in of detail than a major step forward, because it is already accepted that such radio sources are subject to evolution, and the associated problem has seemed to be to explain how and why this evolution occurs. It is clearly a very important result, because we know from studies of our own and other radio quiet galaxies that evolution simply does not occur for the stellar population at anything like the rate required by the observed evolutionary effects in radio galaxies (that is, on a time scale of 10^9 years). Either radio galaxies as a whole age faster than "normal" galaxies, or the radio component itself ages rapidly compared with the ageing of the stars in the same galaxy.

Rowan-Robinson has studied the sources of the third Cambridge survey. Other surveys, notably the Parkes at high energies but including several studies of weaker radio galaxies, have all pointed to the same conclusion; the best suggestion that the theorists have been able to offer has been that the radio sources are ejected from the nuclei of radio galaxies, and then evolve separately from their parents. Although this idea explains, in an arm waving way, why so many radio sources are double, often with one centre of intensity on each side of the associated optical galaxy, nobody has been able to explain quantitatively the way in which plasma could be ejected from the galactic nucleus and interact with the intergalactic medium to produce the sort of radio source which we see. In particular, even out to a distance of 10^6 light years, ejected matter should be more strongly influenced by the gravitational attraction of the parent galaxy than by the evolution of the expanding universe.

But last week a completely new model for radio galaxies and quasars, which can account for their evolution and explains the origin of their energy without running into the problems involved in the ejected plasma model, was put forward by M. J. Rees, of the Institute of Theoretical

Astronomy in Cambridge (*Nature*, **229**, 312; 1971). Rees proposed that the energy in these sources derives fundamentally from the collapse of pulsar-like or other sources, because gravitational energy seems the only source large enough to fill the observational requirements. Unlike other models, however, the latest proposal removes this energy from the nucleus of a galaxy or quasar in the form of low frequency electromagnetic radiation, and not as matter or as high energy radiation.

Rees's model derives directly from work which has been carried out on pulsars, from which it has become apparent that as much as 40 per cent of the rest energy of a collapsing star can be removed by rotation in the form of low frequency electromagnetic waves. Such radiation, having a frequency lower than the plasma frequency of interstellar, and even intergalactic, plasma will expand to produce a cavity containing radiation and relativistic particles, but no plasma. The radiation which we observe could then originate from the interaction of the relativistic particles with this low frequency radiation, producing a hybrid which Rees terms "synchro-Compton emission". It is clear that Rees's model is not only plausible, but produces some remarkable coincidences with the observations.

The energy which goes into the electrons trapped in the cavity gives a spectrum strikingly like that of a typical non-thermal source, even including the break at around 1 BeV which usually requires a very complicated interpretation. Furthermore, under certain conditions the low frequency radiation can be beamed by a self-collimating effect, the external plasma acting as a curved wave guide. This could not only produce the symmetry seen in many sources, but can be extreme enough to produce the jets seen in a few more unusual objects. To be sure, some of this agreement with the observations is so far known only to be possible, and is not a unique requirement of the basic postulates of the model. But the agreement is striking enough to encourage redoubled efforts by observers and theoreticians along the lines indicated by Rees.

As this idea stems from the re-thinking which astronomers have had forced on them by the discovery of pulsars, it is pleasing that these objects could be the sources of the low frequency radiation. Moreover, the short term variability of many sources is temptingly like the behaviour we would expect as new pulsars are formed explosively in the nuclei of radio galaxies and quasars. But even a much more extreme object, such as the massive rotating disk which Lynden-Bell has proposed as the energy source for a galactic nucleus (*Nature*, **223**, 690; 1969), could be the progenitor of the required low frequency electromagnetic waves. It is indeed fortunate that just when the evidence implying rapid evolution of radio sources has become overwhelmingly clear (unless we are prepared to dismiss all the widely held theories of cosmology), a model which can explain this evolution has appeared.

SOMATIC CELL GENETICS

Exploiting Hybrid Cells

from our Cell Biology Correspondent

THE contents lists of such journals as the *Proceedings of the National Academy of Sciences* provide a rough and ready, but nonetheless reliable, guide to the burgeoning areas of biology. And on this criterion somatic cell genetics, stemming from Weiss and Green's discovery that man-mouse somatic cell hybrids preferentially shed human chromosomes and Watkins and Harris's finding that inactivated Sendai virus acts as a general agent for mediating cell fusion, is quite obviously such an area. The exploitation of these twin discoveries has in the past few years revealed the chromosomal localization of several human, structural genes and has provided human geneticists with an invaluable adjunct to conventional pedigree analysis. For example, both pedigree analyses and somatic cell genetics indicate that the structural gene loci which specify human glucose-6-phosphate dehydrogenase (G6PD) and hypoxanthine:guanine phosphoribosyltransferase (HGPRT) are linked on the human X chromosome.

Such an established gene linkage group is to a geneticist little more than a challenge; having proven two genes are on one chromosome he immediately asks how closely are they linked and how many map units separate them? And to judge from the work of Miller, Cook, Meera-Khan, Shin and Siniscalco (*Proc. US Nat. Acad. Sci.*, **68**, 116; 1971), somatic cell hybrids may provide a new method for tackling such questions. They derived six hybrid lines by fusing murine cells, deficient in HGPRT, with human cells with this enzyme and then growing the hybrids in a selective medium in which, to survive, the cells must retain the human HGPRT gene and, therefore, at least part of the human X chromosome. Of course, if the G6PD gene is closely linked to the HGPRT gene on that chromosome one would anticipate that the surviving hybrids would have both these human enzymes. Miller *et al.* found, however, that in forty-seven of the 105 clones derived from four of their six hybrid lines there was no detectable G6PD activity. The simplest explanation of this unexpected observation is that these two genes are widely separated on the human X chromosome such that breakages in the X chromosome frequently separate them, and thereafter they are selected for independently. There are, of course, alternative and more recondite explanations, but Miller and his colleagues offer convincing arguments against all of them. They seem to have had the good fortune to be studying two weakly linked, widely separated genes but, as they note by treating cells with agents which induce chromosome breakages, it may be possible to establish map distances, not to mention gene orders, between more closely linked

loci by the same approach. Clearly, the exploitation of hybrid for the formal genetic analysis of somatic cells is moving from its infancy.

In the same issue of the *Proceedings* (*ibid.*, 82), Kusano, Long and Green report the selection of a new suite of human-mouse hybrid cells which retain the human gene for adenine phosphoribosyltransferase (APRT) in spite of having lost all the biarmed human chromosomes. These cells were obtained by fusing mouse 3T6 cells lacking APRT activity with wild type human, diploid fibroblasts and growing the heterokaryons in a medium containing the antibiotic alanosine which inhibits endogenous synthesis of adenylic acid. Only cells retaining human APRT and therefore capable of taking up adenine from their medium survive. Such survivors shed the human biarmed chromo-

somes but retain the human acrocentric chromosomes. They do not contain detectable murine APRT but have the human enzyme, the gene for which must either reside on an acrocentric chromosome or else some translocation or other rearrangement involving the APRT gene must have occurred in all the survivors. By comparing the human chromosomes in those hybrids which have APRT with a line, Kusano *et al.* have selected from them, which has lost this enzyme, it should prove possible to assign unambiguously the human APRT gene to a particular human, acrocentric chromosome. Further, these hybrids are ideal material for establishing linkages between this gene and other markers and perhaps eventually such linkage groups will be mapped by the methods Miller *et al.* are developing.

Controlling Cellular DNA Synthesis

IN next Wednesday's *Nature New Biology*, J. Salas and H. Green report a pioneering set of experiments which may prove to be the first step in the identification and isolation of proteins which act as switches controlling cellular DNA replication. Recently, increasing numbers of teams have begun attempts to elucidate the nature and function of the factors in serum which induce cultures of cells that have reached their saturation density, beyond which there is no appreciable increase in cell number, to undergo further rounds of division. So far, however, they have remarkably little to show for their efforts and that may have been one of the reasons which led Salas and Green to approach the problem of the control of cellular DNA synthesis in an apparently novel way.

Recently Alberts has devised a method for attaching DNA to cellulose columns and has selected, from extracts of bacteria, proteins with an affinity for DNA. Salas and Green have adopted this procedure, immobilizing calf thymus DNA to cellulose, to fractionate the DNA-binding proteins of a line of mouse 3T6 cells. The argument is, of course, that proteins which bind to DNA are much more likely to play a part in DNA metabolism than those which fail to bind.

After isolating the DNA-binding proteins from exponentially dividing and stationary cultures of 3T6 cells, which had been allowed to incorporate labelled amino-acids, Salas and Green analysed them by polyacrylamide gel electrophoresis. As might be expected, the electrophoretograms revealed a complex pattern of proteins, but eight chief components (P1-P8) were discerned, and the amounts of three of these, P1, P2 and P6, seemed to be correlated with the state of growth of the cells. P6 occurred in large amounts in dividing but not stationary

cells, and the amount of P1 and P2 was inversely correlated with cell division.

By comparing the amount of labelled amino-acid incorporated into these proteins by cells blocked in the stage of DNA synthesis, by cells moving through DNA synthesis and by cells during the transition from the resting to the dividing state, Salas and Green have clear evidence that the synthesis of P6 correlates with DNA replication. Because P6 contains tryptophan, as do P1 and P2, the suggestion that any of these proteins are histones can be eliminated. P6 may, however, be some other protein involved in maintaining the structure of chromatin.

The pattern of labelling of P2 in cells at various stages in the cell cycle is complex and is, until more data are available, not readily interpretable. The pattern of labelling of P1, on the other hand, is quite compatible with the suggestion that it may be a molecule which prevents the onset of DNA synthesis. It is synthesized in large amounts in resting cells but hardly at all in dividing cells. Cells respond to serum starvation by making more P1, and serum is known to contain a substance necessary for the initiation of DNA synthesis. When cells are artificially held in the stage of DNA synthesis the synthesis of P1 cannot be detected, and, finally, when cells pass from a resting to a dividing state the synthesis of P1 declines to almost nil and this decline probably precedes the replication of DNA and synthesis of P6. Salas and Green have already begun similar experiments with a 3T3 line of mouse cells, which is more susceptible to the inhibition of cell division by cell contact, and with cells transformed by oncogenic viruses. They look like uncovering a long and fascinating story which may ultimately reveal several facets of the mechanism of cellular growth control.

BACTERIAL DNA

Coli Coil

from our Molecular Biology Correspondent

AN important development, which should provide a new direction for studies on control of transcription, has been described by Stonington and Pettijohn (*Proc. US Nat. Acad. Sci.*, **68**, 6; 1971). What they have done is to isolate as defined particles the nuclear bodies of *Escherichia coli*. The secret lies in the use of fresh exponential phase cells, gentle lysis with lysozyme and rapid isolation of the particles by a brief centrifugation through a sucrose gradient. The product after extraction from the cytoplasm is stable, sediments at 3200S and has the low viscosity expected for a compact globule. It comprises 80 per cent DNA, the remainder being RNA and protein. The RNA is known from earlier work to be made up in the main of growing messenger and ribosomal chains. The protein is almost entirely RNA polymerase, and comparison of the gel electrophoresis pattern with that of the standard polymerase preparation reveals the presence of the α , β and β' chains, but not of σ -factor, in accordance with the current view that this is released after initiation.

Treatment of the complex with ribonuclease causes it to erupt into linear DNA with a huge increase in viscosity. The same effect is elicited by sodium dodecyl sulphate, but not by proteolytic enzymes. It thus seems that the RNA plays a part in stabilizing the particle and the same may or may not be true of the protein. The nuclear particles are reportedly good templates for RNA polymerase, and it is unavoidable to inquire what attributes they might have in common with chromatin, the properties of which are allegedly controlled in part by endogenous RNA. The observations of Stonington and Pettijohn also add point to the attempts of Lerman and his colleagues—described recently at a meeting of the British Biophysical Society (see *Nature*, **229**, 12; 1971) and in an abstract (*Proc. US Nat. Acad. Sci.*, **66**, 242; 1970)—to characterize a compact form of DNA generated under special conditions selected to simulate them in the cell.

A compact, supercoiled DNA is also found in plasmids of *E. coli*, which are extra-chromosomal bodies, containing a small proportion of protein. I recently drew attention to the work of Clewell and Helinski on one of these (colicinogenic factor E_1), in which it was shown that the supercoil winding was released by introduction of a single strand break apparently by a latent nuclease associated with the DNA. These observations have now been extended in work from the same laboratory (Blair *et al.*, *ibid.*, **68**, 210; 1971) to another colicinogenic factor, E_2 . As with E_1 , treatment with

pronase, or a denaturing detergent, inhibited the relaxation effect. By contrast with E_1 , heat treatment of E_2 substantially prevented relaxation, while leading to the loss of the protein from the supercoiled fraction. This seems to establish beyond reasonable doubt that the DNA in the plasmid is associated with a nicking enzyme that can be inactivated by proteolysis or denaturation.

In order to determine whether the break occurs in the light ("Watson") or heavy ("Crick") strand, Blair *et al.* have made use of a procedure introduced by Hradeczná and Szybalski involving isopycnic centrifugation in the presence of poly (U,G), which has high affinity for the heavy strand. The circular and linear strands are first separated by sucrose-gradient sedimentation at alkaline pH. In this way it was established that Watson is intact and Crick ruptured. A single-strand break must be supposed to precede replication, and it is to be noted

that Gilbert and Dresser have given evidence that the strand broken in induction of λ -prophage is also the Crick strand.

For anybody with a serious interest in supercoiling, another surpassingly accomplished article by Bauer and Vinograd (*J. Mol. Biol.*, **54**, 281; 1970) is mandatory reading. This concerns the relation between supercoiling, as controlled by dye intercalation, and buoyant density. The insertion of ethidium bromide into the DNA double helix has two effects. One is that the helix behaves as a stiffer and a more slender rod in solution. The second is that the intercalation causes a partial uncoiling of the helix at the point of insertion, and in closed circular DNAs this causes a reduction in the degree of supercoiling which in turn changes the buoyant density of DNA. The diagnostic application of the phenomenon for determining whether drugs, antibiotics and the like bind by intercalation or otherwise is developed by Waring (*ibid.*, 247).

New Assays for Old

ONE of the advantages of conventional radioimmunoassay is its high specificity—the antibody produced against the hormone concerned frequently shows little or no cross-reaction with quite closely related compounds. This feature is particularly important in biological assay because *in vivo* and *in vitro* degradation products are frequently present in extracts. Equally, however, if there are closely related compounds of interest in addition to the one under study, this antibody specificity necessitates producing separate specific antisera for immunoassay—or at least this is the conventional approach.

Giese, Nielsen and Jørgensen now show in next Wednesday's *Nature New Biology* that this approach may not be essential. They have taken advantage of the heterogeneity of antibodies for assay of materials which are apparently non-cross-reacting. Their investigation concerned antibodies against angiotensins I and II which do not usually cross-react when tested by conventional assay. Thus, displacement of labelled angiotensin II from its specific antibody by unlabelled angiotensin I is usually less than 1 per cent. Giese *et al.*, however, now show that if the same anti-angiotensin II antibody is tested using labelled angiotensin I, not only do quite a high proportion of sera bind the label (albeit at a much lower dilution) but also that this binding is relatively specific; that is the labelled angiotensin I is displaced from antibody much more readily by unlabelled angiotensin I than by unlabelled angiotensin II.

The practical consequence of this in angiotensin immunoassay may be that radioimmunoassay of angiotensin I can be performed using the more readily

available anti-angiotensin II sera. It will be of great interest to see whether this system can be extended to other antibodies, for if the sensitivity and specificity of assay can be made high enough this could be a very important contribution to the assay of closely related compounds such as steroids or peptide hormones of different species, particularly where antisera are difficult to raise.

Ng and Vane showed in 1967 (*Nature*, **216**, 762) that it is the lung and not the blood which is the important site of angiotensin I conversion *in vivo* to the biologically active component of the renin-angiotensin system, angiotensin II. Bakke and Reynard have now taken steps towards characterization of a converting enzyme in the lung by isolating from lung homogenates a material which is relatively free from enzymes which destroy angiotensin, collectively referred to as "angiotensinases". In next Wednesday's *Nature New Biology*, they present some of their preliminary data on its characteristics as tested in their *in vitro* assay system, with particular reference to its metal dependence, pH optimum and relationship to plasma converting enzyme. Several features of some interest emerge at this stage, in particular the observation that converting enzyme activity is apparently membrane bound. Moreover, it seems to have a relatively slow rate of angiotensin I converting activity when compared with the highly active *in vivo* system. But it would be premature to draw too firm conclusions at this stage and further understanding must await better purification. Precise specificity studies are also needed to ensure that this material is the same as the mechanism responsible for *in vivo* angiotensin I conversion.

PRE-CAMBRIAN

Holocene Activity?

from our Geomagnetism Correspondent

It is not very often that 3,000 year old man gets a chance to make a contribution to twentieth century geology; and seldom do engineering and archaeology combine to suggest a fundamental reassessment of geological activity in Pre-Cambrian areas. The Volta River Project in Ghana, however, has provided examples of not one but both of these unlikely events, as Thompson has now described (*Bull. Geol. Soc. Amer.*, **81**, 3759; 1970).

Detailed study of the Volta River to select a suitable site for a dam was begun in 1959. The reason for choosing the Volta was simply that it is Ghana's largest water course—its principal stem and many tributaries provide a drainage pattern which covers about 75 per cent of the country's surface area. Other streams are relatively short; and most of them flow west of Accra where they run down to the Gulf of Guinea across a gently sloping plain developed from the oldest Pre-Cambrian rocks. Much of the lower course of the Volta also flows across Pre-Cambrian rocks; but there the resemblance ends. For, whereas the trends of the other Ghanaian rivers are controlled by the structure of the bed-rock, it has been shown that the course of the Volta is not.

And that is not the only strange feature of the lower Volta. At Ajena, a few miles upstream from where the dam was finally sited (Akosombo), the river was only about 5 feet deep (before the dam was built); and 11 miles downstream at Senchi the water was so shallow that it could be crossed by wading. Between these points, however, the stream bed dips rapidly to give a maximum depth of about 200 feet and thus assumes what Thompson calls a "lake-like condition" with a jagged bottom profile. It is clear therefore that whatever other geological process might have produced this part of the river basin, it was certainly not normal erosion.

So what was the origin of this unusual river bed? Surprisingly, the clues come chiefly from history and archaeology. Legends to the effect that Earth tremors have caused panic among the local tribes have been passed from generation to generation to become part of the cultural history of the region. Legends alone do not, of course, rate very highly as scientific evidence; but backed by the record of a real earthquake which occurred near Accra in 1937, they suggest that earthquake activity is no stranger to the area in recent times.

In support of this view, Thompson also quotes a nice piece of archaeological evidence. Before construction of the dam was begun several small rock islands protruded above the water surface,

but, during construction, it was necessary to lower the water surface by about 35 feet, a process which revealed, at 32 feet below the normal water level, a man made carving which was dated as 3,000 years old. This would seem to indicate that one side of the Accra fault, which roughly coincides with the Ghanaian coast along the Gulf of Guinea and which marks the downstream boundary of the "lake-like" basin, must have undergone a vertical displacement of about 32 feet during the past 3,000 years. In other words, the deep basin and its peculiar profile were almost certainly formed by recent (post-Pleistocene) tectonic activity.

As a result of these discoveries during construction, the design of the Volta dam was rapidly amended to allow greater resistance to earthquakes. But the most interesting part of this story is why such a possibility was not foreseen. The reason is, of course, that the lower Volta runs over Pre-Cambrian rocks; and Pre-Cambrian regions are traditionally thought of as stable areas free from faulting and thus not subject to earthquakes. Perhaps, as Thompson suggests, this view is outdated, especially because there is also evidence of recent activity in the Brazilian Pre-Cambrian shield. Near São Paulo, for example, road cuttings have exposed strong displacements of Pleistocene and Holocene continental basin fills by faults which project upwards through the Pre-Cambrian

schists and gneisses and strongly offset the younger material. In the light of this evidence Thompson goes so far as to suggest that many of the Earth's Pre-Cambrian areas should now be classified as earthquake hazards "as severe as California".

PHOTOSYNTHESIS

Enhancement Annulled

by our Plant Physiology Correspondent

THE structure of plastids is so closely bound up with their function that it is hardly surprising that recent experiments have shown the well known enhancement of photosynthesis by short wavelength light to be annulled, when chloroplasts were converted from the lamellar to the homogeneous state. Nevertheless, it is a great deal easier to make the insides of chloroplasts homogeneous than it is to explain what changes take place in their biochemistry after the transformation. The answers to some of the questions posed may considerably advance our understanding of the photosynthetic machinery.

Chloroplasts in most flowering plants have a characteristic appearance; ovoid organelles containing organized arrays of membranes. These membranes are of two sorts, the grana, which are deeply pigmented and look like cylin-

Membrane Protein and Sodium Inactivation

THE action potential of nerve fibres results from a large transient increase in the sodium permeability of the membrane which gives rise to a flow of sodium ions from the external medium into the interior of the fibre. The increase in permeability is short lived; it is abolished within a few milliseconds by a process known as inactivation. This process is largely responsible for the short duration of the nervous impulse and for the well known refractory period following each action potential. Very little is so far known, however, about the molecular events in the membrane which are responsible for the inactivation of the sodium permeability. E. Rojas and C. Armstrong now show in next Wednesday's *Nature New Biology* that inactivation depends on the intactness of a membrane protein; internal treatment of nerve fibres with the proteolytic enzyme pronase completely eliminates inactivation.

Intracellular perfusion of giant axons of the Chilean squid *Dosidicus gigas* (diameter more than 1 mm) was carried out using the well established method consisting of removing part of the axoplasm and perfusing the interior of

the fibre with an artificial salt solution. The membrane currents were recorded with the voltage clamp technique. 30 min perfusion with a salt solution containing the enzyme pronase (1 mg ml.⁻¹) drastically altered the membrane currents—the normal transient sodium inward current was replaced by a sustained inward current which declined only very little during a 15 ms pulse. It was most clearly seen after eliminating the overlapping potassium current by tetraethylammonium chloride. At the end of the pulse a large inward tail current occurred. Rojas and Armstrong found that the sustained inward current and the tail current could be blocked by tetrodotoxin, the specific inhibitor of the sodium permeability.

The effect of pronase on sodium inactivation was found to be fairly selective. Activation of the sodium permeability remained essentially intact. The potassium permeability was normal provided the treatment with pronase was not too prolonged. Thus, Rojas and Armstrong's work supports the idea that sodium and potassium ions pass through the membrane in separate channels.

dricol piles of coins, and the fretwork, a loose arrangement of membranes which lie over, around and between the grana. There is a clear division of labour between these two types of membrane; the grana are coloured by the photosynthetic pigment, chlorophyll, and all the light reactions of photosynthesis leading to the formation of high energy phosphate compounds and a source of reducing power are located on these membranes. The dark reactions which lead ultimately to the synthesis of carbohydrates seem to be confined to the stroma of the chloroplast, the amorphous matrix in which the membranes lie.

Chloroplasts, however, do not always present this hardly simple but nonetheless organized picture. Sometimes the inside of the plastid appears completely homogeneous under the microscope and no grana can be seen. It is possible to cause this transformation artificially by illuminating plants with red light for several hours (T. Punnett, *J. Cell. Biol.*, **35**, 108A; 1967). It seemed therefore to Dr Punnett that it would be interesting to find out what happens to the photosynthetic functions of the chloroplast after inducing this structural change.

He examined the enhancement of photosynthesis by short wavelength light in homogeneous and granulated chloroplasts (*Science*, **171**, 284; 1971). The reactions which lead principally to the formation of a source of photosynthetic reducing power are currently believed to be initiated by far-red light (700 nm). This light is inefficient in promoting those reactions which lead to the formation of high energy phosphate compounds, however, and for maximum photosynthetic efficiency the far-red light must be supplemented by light of shorter wavelengths. This is termed photosynthetic enhancement.

Punnett found that in homogeneous chloroplasts, enhancement, which is normally about 30 per cent, was reduced almost to zero. Punnett has two theories to account for this; first, there may be a shift in the partitioning of light energy absorbed by the chloroplast pigments so that nearly equal amounts of energy are delivered to the long and to the short wavelength light reaction. In these conditions, photosynthetic enhancement will, of course, approach zero. The second possibility is that the mechanism of photosynthesis switches from a reaction involving two photosystems to a simpler form involving but one photoact. It is impossible to tell at present which of these possibilities is most likely, but it seems certain that light activated ion transport is in some way involved. The eventual elucidation of how ion transport alters as plastid structure changes should add a fascinating chapter to this story.

GRAVITATIONAL CONSTANT

Measurements Refined

THE possibility of the gravitational "constant" G not really being a constant was first discussed by Dirac in 1938 (*Proc. Roy. Soc., A*, **165**, 199). Since that time, there have been several conjectures made on the variation of G , and an estimate for the magnitude of the possible variation with time was given by Dicke in 1962 (*Rev. Mod. Phys.*, **34**, 110; 1962, and *Science*, **138**, 658; 1962). He postulated on theoretical grounds that the value of $1 \frac{dG}{dt}$ could be decreasing at the rate of 4×10^{-11} per year.

A group at MIT's Haystack Observatory now report a continuing series of measurements that aim at determining the time variation of G (I. I. Shapiro *et al.*, *Phys. Rev. Lett.*, **26**, 27; 1971). A decrease in the gravitational constant implies an increase in the orbital planetary periods and, for six years, the MIT group has been involved in measuring these periods. The group use a planetary radar system and regular measurements are taken of radar-echo time delays between Earth and Venus and Earth and Mercury. The data for Earth and Mer-

cury, which were accumulated chiefly during the past three years, are more significant than the earlier work because Mercury has an average orbital angular velocity five times that of the Earth.

To analyse their data, the MIT group take an *ad hoc* model assuming that each planet obeys the equations of motion that follow from the Schwarzschild metric for the Sun and from Newtonian perturbations attributable to the Moon and other planets. In this model, however, G is

replaced by $G_0 + \frac{dG_0}{dt}(d - t_0)$. A com-

puter program is used to fit the model to the data and to extract values for eighteen variable parameters. Values for seventeen of the parameters (the eight-

eenth being $\frac{1}{G} \frac{dG}{dt}$) were consistent with

previous work at MIT, and statistical tests showed the data to be internally

consistent. The value of $\frac{1}{G} \frac{dG}{dt}$ obtained

was less than the expected standard error, and an upper limit of 4×10^{-10} per year is quoted, an order of magnitude larger than Dicke's prediction.

Because the experiment is still in pro-

Chemistry and Hair Colouring

A GOOD example of some basic research in chemistry which will probably have a definite industrial application in the near future is described in an article in next Monday's *Nature Physical Science*. M. M. Breuer reports work done at the Unilever Research Laboratory at Isleworth, Middlesex, to elucidate the reasons why differing quantities of aromatic and aliphatic compounds are absorbed from solution by human hair. The uptake of aliphatic compounds such as ethanol is found to be at least ten times lower than the corresponding figure for aromatic compounds such as the phenols.

Investigations of this type are of considerable importance in the development of more efficient hair preparations and Breuer reports a systematic study which suggests that aromatic compounds are absorbed more easily because of a dipole-induced dipole interaction between the peptide groups of the hair protein (keratin) and the easily polarized aromatic molecules. The formation of similar association complexes between molecules in solution is already well established (see, for example, Homer and Cooke, *J. Chem. Soc. A*, 2862; 1969).

Breuer's conclusion about the nature of the bonding interaction was reached after a number of other possibilities had been eliminated. Experiments showed, for example, that the aliphatic 1,4-dihydroxycyclohexane is not absorbed by hair even from a saturated solution. If this

behaviour is compared with the known appreciable uptake of hydroquinone (aromatic), several bonding possibilities can be ruled out. The existence of hydrophobic bonds, which are formed by the elimination of a water molecule, would imply that the absorption of the two compounds should be similar—the hydrophobic bond energy is approximately proportional to the number of hydrocarbon groups in the absorbed molecule and this number is the same for both 1,4-dihydroxycyclohexane and hydroquinone. The possibility of the involvement of hydrogen bonds is also negligible, Breuer suggests, because benzene, which contains none of the hydroxyl groups characteristic of the phenols, is also found to bind easily to keratin.

Support is lent to Breuer's proposal by the work of Matson *et al.* (for example, *J. Colloid Interf. Sci.*, **31**, 116; 1969) on the absorption of phenols on activated carbon surfaces. They found that the principal adsorption sites for phenol molecules are the surface carbonyl groups and, by infrared spectroscopy, that the stretching mode of the C—O—H linkage was unchanged after adsorption, thus vitiating the hydrogen bond theory. Breuer completes his article by comparing the calculated binding constants of several phenols to wool with their measured polarizabilities; these turn out to be consistent with his approach to the bonding problem.

gress, the accuracy in the determination of $\frac{1}{G} \frac{dG}{dt}$ will improve with time. Shapiro *et al.* calculate that a further five years would bring the accuracy of the experiment to the order of magnitude suggested by Dicke. Similar observations made elsewhere could, of course, reduce this delay. Shapiro *et al.* suggest, however, that the determination of $\frac{1}{G} \frac{dG}{dt}$ from the lunar laser ranging experiment set up by the crew of Apollo 11 seems to be affected at present by complications caused by the Earth/Moon tidal interaction.

Some of the aspects associated with having a slowly varying gravitational constant have been considered by Dicke and Peebles (*Space Sci. Rev.*, **4**, 419; 1965). Among the effects enumerated by these workers, the following two quantitative values, based on Dicke's estimate of the possible rate of change of G , are of considerable interest. First, a steadily decreasing gravitational constant would make computed stellar ages too large by a factor of two or three; second, because the Sun's luminosity is proportional to the power of G^7 or G^8 , it would have been considerably more luminous in the past. Thus, if primitive life arose on Earth 3×10^9 years ago, the average Earth temperature at that time would have approached the boiling point of water. These and other uncertainties will be clarified if a value for the time variation of the gravitational constant is ultimately found.

SOLID STATE PHYSICS

Condensed Matter

from a Correspondent

AT the eighth annual solid state physics conference held at the University of Manchester from January 5-7, the topics covered could be more properly described as "condensed matter" rather than "solid state" because a symposium on liquids was one of three that were organized there.

Some particularly interesting work on techniques reported involved, on the one hand, methods of electron spectroscopy and, on the other, high voltage electron microscopy with particular reference to studies of radiation damage. Much of the pioneering work in the first of these fields has been carried out by Professor K. Siegbahn and his colleagues at the Institute of Physics at Uppsala and Dr C. Nordling from this group gave a fascinating account of this work, ranging from a study of water vapour to a discussion of electron transfer in transition metal carbides. Related theory of X-ray and ultraviolet spectroscopy was discussed in general terms by Professor I. Hedin (Chalmers University of Technology), and it seems fair to say that all the principal

elements in the theory are now known and that the data can now provide precise information on the dominant, underlying one-electron effects. This does not mean that the many body effects or the role of the core in the soft X-ray emission experiments are not of interest, but that densities of electronic energy states from this type of measurement are still needed. This lack of data is particularly evident in disordered systems, where the classic crystalline state experiments are not applicable. There was substantial interest at the meeting in this area of research.

In the liquids symposium, one of the highlights was undoubtedly the contribution by Dr M. Ross (Lawrence Radiation Laboratory, Livermore), who discussed the exciting new information that can be obtained from shock wave studies on liquids. Here, the high pressures and the tremendously high temperatures are opening up a whole new field of research. Related work on the critical region in liquid metals was dealt with by Dr R. G. Ross (University of East Anglia) who stressed the relation between the critical point and the metal insulator transition. The metal insulator transition continues

to be an area of considerable interest—a plethora of transitions is now described, for example, Witner, Mott, Anderson and Hubbard—but it is difficult to obtain decisive experimental evidence for such transitions.

Professor C. Domb (King's College, London), focusing on other aspects of critical phenomena, gave a lucid review of an area in which critical behaviour can now be understood, and a tremendous pattern is being revealed. Although so far the pattern is clear the underlying justification for scaling theories is still not sufficiently basic. But such deeper understanding is hardly likely to alter the established relationships between the critical indices.

It is worth emphasizing that three areas that were particularly prominent at the meeting—electron transport in semiconductors, amorphous materials and magnetism—were no doubt stimulated by technological interest. The resurgence of interest in magnetism, both because of its technological importance and because its fundamental phenomena involve the correlations between electrons so basically, was evident.

Cyclic Delocalization of Electrons

ONE of the successes in the field of theoretical chemistry has been the understanding of the structure and properties of aromatic compounds. The term aromaticity was originally confined to a class of molecules, the prototype of which was benzene. It was shown by Hückel many years ago that most of their properties could be interpreted in terms of the delocalization of π electrons and that aromatic compounds obeyed the rule which states that $(4n+2)$ numbered rings have stable electron configurations. The success of Hückel's molecular orbital theory chiefly arose from the emphasis it placed on orbital symmetry; several later studies emphasized and extended various symmetry aspects of the theory.

In next week's issue of *Nature Physical Science* E. A. Magnusson examines in detail the topological characteristics of electron delocalization in linear and ring systems. He suggests that with the aid of so-called π graphs (delocalization pathways) it is possible to group unsaturated molecules in a systematic manner. Compounds are first classified as "homomorphic" or "heteromorphic"; these terms were first introduced by Craig in the study of phosphonitrilic halides to distinguish systems containing π orbitals all belonging to the same local symmetry species from those which include different species. A further subgrouping is possible depending whether or not all the π -orbitals can be chosen in phase. They are

termed "matched" and "mismatched" systems, and benzene, for example, belongs to the matched class, whereas the hypothetical Möbius benzene belongs to the mismatched class. This classification is important because the two subgroups show different ordering and pattern of orbitals, and thus display Hückel and anti-Hückel behaviour. These differences, in turn, are related to properties such as ring currents, stability, and reactivity. Some unsaturated compounds do not fit into the classification scheme because there are several topologically non-equivalent delocalization pathways. Sandwich compounds such as ferrocene belong to this category and exhibit what is called complex delocalization. A large number of compounds have been classified and discussed in this way.

Magnusson's discussion of the topology of π electron paths is timely and important especially because of the recent emphasis on orbital symmetry in reaction mechanisms as embodied in the Woodward-Hoffmann rules. It now seems that the analysis could be made much simpler by examining the topology of the π electron pathways in transition states. Matched and mismatched transition states, called aromatic and anti-aromatic respectively, exhibit different reactivities and Magnusson's topological classification of π electron systems should be of considerable use to chemists in this context.

GAS REACTIONS

Neutral Beam Kinetics

from our Molecular Physics Correspondent

THE prolonged and, at times, painful evolution of chemical kinetics into an exact science has been measured, not so much by theoretical advance as by the growing determination of experimentalists to stop heating things in a pot and concentrate on the crucial problem of fixing the fundamental action of collision between reagent molecules in some form of direct observation. Although they will surely never see this act with the ease of a nuclear physicist observing particle tracks, the past decade has brought remarkable progress towards liberating experimental gas kinetics from the pervasive and sometimes cruel deceptions caused by trace impurities, the walls of the container, secondary reactions and, not least, the Boltzmann distribution of energies itself.

Two instruments, the molecular beam apparatus and its relative the mass spectrometer, have contributed more than any others to this movement; indeed it has long been realized that anybody ingenious enough to couple both these into a single instrument for reaction and analysis would have something like the answer to the kineticist's prayer. What is perhaps the first really successful application of the combined system to the study of neutral atom-molecule reactions now seems to have been achieved by S. N. Foner and R. L. Hudson, of Johns Hopkins University (*J. Chem. Phys.*, **53**, 4377; 1970).

In the ideal molecular beam apparatus reactive molecules or atoms would be fired at each other in streams which are highly defined in both position and velocity and almost innocent of all self-collisions. To the extent that this can be achieved in an actual apparatus, the statistical noise in the outcome can be treated in terms of the dynamics of the reactive scattering alone, while, at the same time, the product particles can be whisked into an analyser with little chance of secondary reaction. Measurement of the identity, recoil velocity, and angular spread of the products can then be attempted. Unhappily, although this sequence sounds straightforward on paper, there is much bitter experience on both sides of the Atlantic to show that, unless the beam definition and intensity and the detector selectivity and signal/noise ratio combine to a certain threshold, all the elaborate vacuum and electronic engineering necessary will be in vain. Although most workers in the field have always looked to the mass spectrometer for their salvation, the intensities of beam available with neutral molecules have never been sufficient to allow a further loss of signal by a factor of perhaps a thousand in ionization at the

mass spectrometer stage. As a result ion-molecule reactions have gained a somewhat undeserved prominence and those laboratories remaining faithful to neutral systems have developed an unhealthy dependence on the few beam reactions which can be run with unsophisticated detectors, chiefly those of alkali metals and halogen compounds.

The apparatus of Foner and Hudson, developed out of many years' experience with the mass spectrometry of unstable species, brings a variety of ordinary atom-molecule reactions within the scope of crossed-beam mass-spectrometric detection for the first time. This is achieved by crossing two relatively ill defined beams at high intensity and making a calculated sacrifice of the scattering-angle information usually sought, for the sake of increased detector efficiency. This is hardly too great a price to pay, for, with a consequent increase of a factor 10^4 in detector signal over that obtained in conventional crossed beam arrangements and with products discriminated by both

mass and ionization potential, the information to be gained is still very considerable. Foner and Hudson describe a whole gamut of reactions, resulting from Cl, O or H atoms in one beam and hydrocarbons, hydrazines or oxides of nitrogen in the other. The different butyl radicals are produced in a very clean reaction of chlorine atoms with butanes, the classic reaction of H with NO_2 is re-examined and a bizarre reaction of O atoms with hydrazine is reported in which the oxygen makes off with two hydrogens abstracted simultaneously from opposite ends of the molecule. In all cases ionization energies of the species involved are obtained at no extra cost.

Although much remains to be learned about the physics of these processes, it is gratifying that some of the elementary atom and free radical reactions which are familiar only as equations in the complicated hypothetical schemes of the textbooks should now be under scrutiny as truly elementary events.

Why do Magnetic Anomalies Weaken?

THE magnetic evidence for seafloor spreading is based on the pattern of the linear magnetic anomalies which lie over and to the sides of mid-oceanic ridges. This pattern correlates well with the dated polarity-time scale from continental rocks up to about 4 million years old; and, because the latter must be produced by reversals of the Earth's magnetic field, there is no reason to suppose that the older marine anomalies are not also reflexions of geomagnetic field behaviour. For this particular exercise, however, the amplitudes of the anomalies are unimportant—it is the wavelengths alone which decide the issue.

The anomaly amplitudes, in fact, are not constant but generally decrease with distance from a ridge. But why? There has been no shortage of possible explanations for this phenomenon; but so far nobody has succeeded in pinning it down to one. One of the earliest suggestions was that the rocks producing the older anomalies are deeper and have a thicker sediment cover and thus are partially shielded magnetically. But it seems probable that this is altogether a too facile explanation; and, in any case, there does not seem to be a correlation of amplitude with sediment thickness where such a possibility has been investigated in detail.

Other suggestions have been more sophisticated but notably short on evidence. Matthews and Bath (*Geophys. J.*, **13**, 349; 1967), for example, thought that the central ridge block might be injected slightly asymmetrically and thus "contaminate" the blocks of opposite polarity on either side. But Harrison (*J. Geophys. Res.*, **73**, 2137; 1968) soon

put an end to this idea by pointing out that this process would almost certainly have obliterated the short magnetic events which are visible in the anomaly pattern.

The most popular explanations invoke some sort of decay of the magnetization in the ocean floor basalt. Chemical alteration is a widely touted mechanism for this; and it is not difficult to imagine what seawater and high pressures might do in this line. But imagination is not enough. Proponents of chemical alteration have always been intuitively convincing but short on specific proof. The problem of decay has, of course, bedevilled palaeomagnetism for many a year; but nobody has been able to explain it properly in physical terms. Indeed, at one stage the whole question was in danger of becoming a universal palaeomagnetic pessimism; but the pessimists were firmly routed by the discovery, from rock magnetism, that at times during the Pre-Cambrian the Earth's magnetic field was as strong as, if not stronger than, it is now.

But in spite of all this, the older marine magnetic anomalies are self-evidently weaker—and some explanation is still required. In next Monday's *Nature Physical Science* S. K. Banerjee, fully appreciating the history of this problem, puts forward a new possibility—decay of magnetization by diffusion of ferrous ions but without chemical alteration. Banerjee's argument is highly theoretical and heavily dependent on uncertain estimates of several physical parameters. For this reason it will be very difficult to obtain direct proof. On the other hand, it does not suffer from the obvious disadvantages of the simpler, perhaps more naive, explanations.

Conserving Rare Plants in Britain

by

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There are several ways in which many rare British plants could be saved from extinction. In this article two members of the Botanical Society of the British Isles set out some criteria for local, national and European action.

IN September 1969 F. H. P. reported to the Botanical Society of the British Isles (BSBI) that, since botanical recording began in the middle of the seventeenth century, about twenty native plant species are believed to have become extinct in Great Britain. He also produced evidence that many more species are in danger of extinction if they are not protected immediately¹.

When the field work for the preparation of the *Atlas of the British Flora*² was being carried out by the BSBI in 1954–60 a thorough survey was made of the past and present distribution of rare species. In the late 1960s a re-survey of the rarest 300 species was made through the county recorders of the BSBI. A combination of these two surveys showed that before 1900 forty-four species (17.4 per cent of the rarest 300) occurred in only one or two 10 km squares of the national grid; by 1930 the number was fifty-nine species (23.3 per cent of the rarest 300), and by 1960 it was ninety-seven species (38.7 per cent of the rarest 300).

Thus about 7 per cent of the native British flora of about 1,500 species may be in danger of extinction, and further species are declining so rapidly that they may shortly be in the same dangerous situation. This is particularly true of species of marshes and wet meadows which are subject to draining. The fritillary, *Fritillaria meleagris*, once known from more than 100 localities, is now known from only eleven (Fig. 1a). The fen orchid, *Liparis loeselii*, once widespread in the fens of East Anglia, occurs in very few localities in that region and grows mostly in dune-slacks in South Wales (Fig. 1b). One of the most attractive weeds of British farmland, the cow-wheat, *Melampyrum arvense*, is on the verge of extinction, surviving in a few hedgerows where it is always under threat from burning or clearance. Once reported from nearly fifty localities, it is now known from only five.

If losses like these are to be halted a comprehensive plan must be prepared and put into action. Some progress has already been made and further measures are proposed. In this article we wish to review the present situation.

Action by Biological Records Centre

First, as much information as possible is being collected about each site of each rare species. The Biological Records Centre of the Nature Conservancy is asking amateur and pro-

fessional botanists who visit any of the sites to complete a simple form on which they record the exact locality, making a sketch map indicating the limits of the population and, where possible, counting the plants. They are asked also for brief ecological notes and, most important, what protection, if any, is already afforded to the site. At the centre the data will be used to acquire a national picture of the state of each species and to decide for each rare species a "threat number" which is based on five criteria: (1) the absolute size of the population(s) in Great Britain; (2) the rate of decline; (3) the attractiveness of the species; (4) the accessibility of the site; and (5) the present conservation status of the site(s).

The threat number will enable us to decide which species are most in need of protection, in consultation with the Conservation Committee of the BSBI. The decisions can be translated into action at the Biological Records Centre, where lists of species and localities classified by counties can be compiled using data processing machinery. The lists will be sent to the appropriate county conservation trust and members of the regional staff of the Nature Conservancy, with a request that they do all in their power to safeguard the localities listed.

Local Action

If the site of a threatened species is already a nature reserve then any management plan for that reserve should take account of the presence of the rare species and, where necessary, research should be carried out to determine what action, if any, is needed to maintain or increase the population. In the absence of research it is usually best to ensure that past management is continued, maintaining the conditions in which the species has survived for so long.

If a locality is not a nature reserve, it is to be hoped that local conservation organizations will try to acquire the site or, if that cannot be done, to ensure that the owner understands its importance and allows management to be carried out where necessary. Local action is most likely to be successful in this respect: personal contact with an owner or tenant can succeed where official letters fail. The BSBI intends to provide a tool for local initiative by producing during the next year a list of all the rare plants of Britain, indicating for each species the past and present distribution (not including exact localities, of course), and the rate and probable causes of decline. The book will be published with the approval of the Conservation Liaison Committee of the Society for the Promotion of Nature Reserves (SPNR), on which the voluntary and professional conservation organizations and the national biological societies are all represented. A statement such as "now only known from two localities in Cornwall" may be valuable ammunition when talking to the farmer who owns one of the localities.

Even when the conservation organizations are successful, and control over a site has been acquired, access may have to be

limited. This may be because constant visits disclose the site of an attractive species to unscrupulous collectors, or because the habitat is fragile and could be destroyed by the trampling of the wellwishers most keen to protect it.

It is surely better, particularly in rapidly developing regions, that local conservation organizations should know the exact localities of the rare species in their area so that they can keep their planning authorities fully informed: the dangers from house building, road widening, pipe laying, drainage schemes and so on are much greater than attacks by a few unscrupulous naturalists. Nevertheless, action would certainly not be complete unless attention were paid to this aspect of the conservation of rare species.

National Action

On a national scale the first need is for legislation. There is no general law against picking or uprooting wild flowers in Great Britain, although most counties have bye-laws which make it an offence to dig up plants in places to which the public has access. These bye-laws are largely forgotten, are totally ineffective and in any case are too blunt a weapon to deal with the problem of particular species in particular places. For some years the Wild Plant Protection Working Party, with members from the SPNR, the BSBI and the Council for Nature, has been working on a bill which would make the picking or uprooting of certain rare species illegal. The threat number will help to determine which species should be included, although if the bill becomes law it is hoped that it will give the minister concerned powers to alter the list on the advice of a panel, whose judgment would be based on frequent re-surveys carried out by the BSBI.

The next requirement is persuasion. An Act of Parliament is needed to give teeth to the other actions which must be taken to bring about a change in attitude to collecting—a change which has been brought about for birds in Britain during the past twenty or thirty years, by a combination of legal action and publicity. The BSBI has made a start by producing a code of conduct for its members—a guide to collecting and

visiting rare or local species. The most important clauses of the code are as follows: (1) Members should not pick or collect any material of nationally rare species as defined in a list published by the society (longer than the list in the proposed Act). (2) Members should not collect specimens from any nature reserve or nature trail without permission. (3) Members should not collect specimens of any species in a locality in which it is scarce. (4) When living material of rare or local species is required for experimental work members should raise it from seed or cuttings wherever possible. The code also warns of the dangers of large numbers of botanists visiting or photographing the site of rare species. The British Lichen Society has already produced a similar code for its members and it is hoped that other national biological societies will do so too. Using particular codes as a basis, the Conservation Liaison Committee hopes to prepare a common code as a guide to all biologists, amateur and professional, who may not be members of national societies but need just as much guidance, for example, members of natural history societies, school teachers, students, and non-taxonomists in university biology departments.

Guidance is required at the local as well as the national level. It is still common in many parts of Britain for competitions to be held for the largest collection of wild flowers which can be made by school children. This can obviously endanger locally rare species, and yet it would be an educational loss if all collecting ceased. As a compromise several local education authorities, with the backing of their local conservation organizations, have produced guides to the collecting of wild flowers in their counties—Brecon, Cambridgeshire and the Isle of Ely, Hertfordshire, Huntingdonshire and Northamptonshire education authorities have done this. The guides usually contain two lists, one of about 250 plants which could be collected with safety, and a second of decorative and beautiful flowers often rare or local which should not be picked.

Botanists generally agree that adequate material of rare species for classical taxonomic studies is already available in British herbaria: it is the cytogeneticists, plant biochemists, population analysts and so on who make the biggest demands

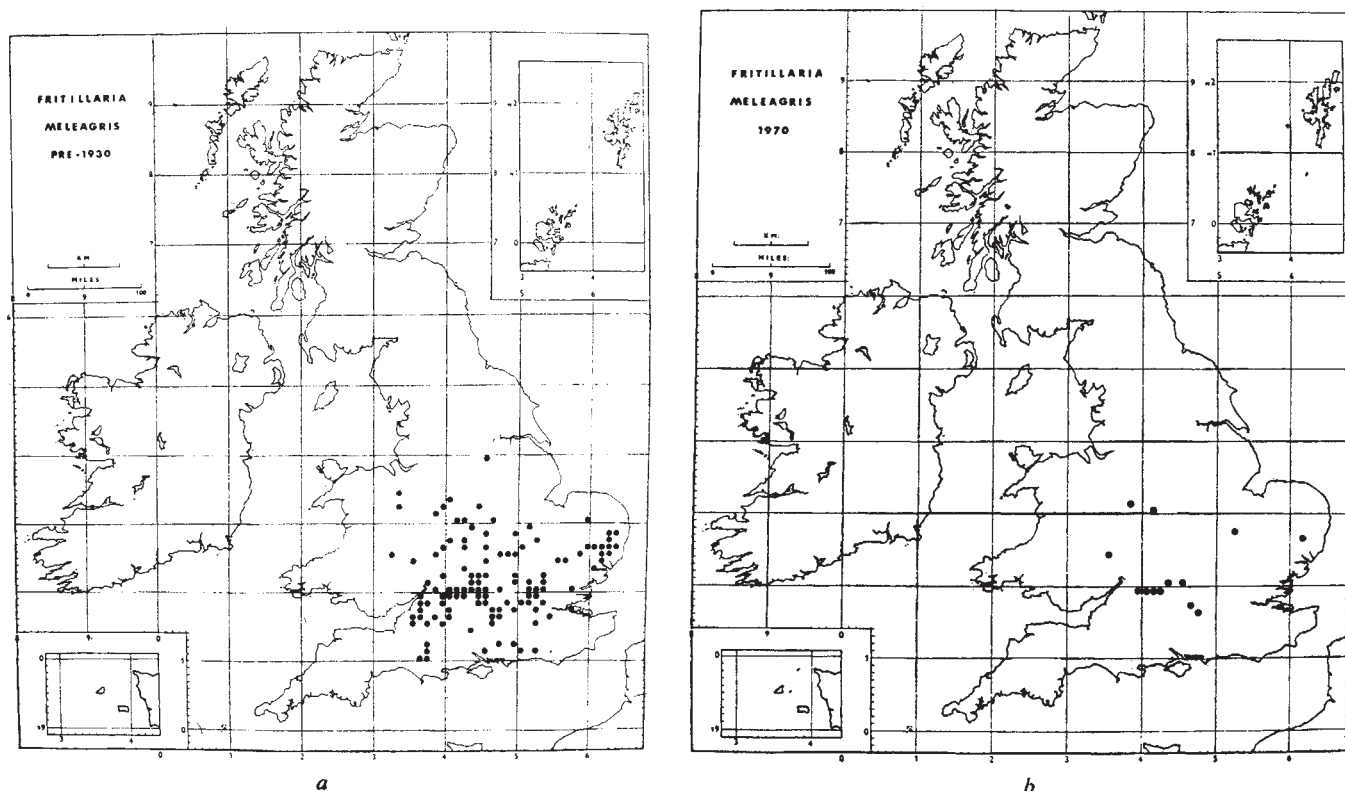


Fig. 1 The distribution of *Fritillaria meleagris* in Britain (a) before 1930, and (b) in 1970.

for living material from the wild. If the BSBI's suggestion that members should raise rare species from seed or propagate them from cuttings wherever possible is to become effective, centres of seeds and cuttings must be established and scientists must be able to find out easily what they contain.

The BSBI has begun discussions with several of the larger botanic gardens on the question of how this problem is to be tackled. In every case the suggestion of cooperation has been warmly welcomed by the gardens. It is hoped that particular botanic gardens will maintain living plants of known provenance of particular species, and that a register of these will be maintained by the BSBI. Anybody wishing to work on any species in the list of those not to be collected would be asked to obtain material for study from the appropriate botanic garden and not from the field.

During the past two years the Royal Botanic Gardens at Kew have developed a seed bank with extensive low temperature storage facilities³. It is agreed that Kew will maintain stocks of seed of rare British species. The intention is that members of the BSBI will collect the necessary material, under guidance, during the next few years. If material from the remaining sites of diminishing rare species is safely in cultivation or stored as viable seed, at least the potential genetical and physiological interest of these usually isolated populations will not be lost to science.

Introductions and Reintroductions

If material from all localities can be propagated successfully, the interests of conservation can be served in another way. If the native site of a rare species is destroyed temporarily, the species can be reintroduced after the danger has passed, from stock known originally to have come from that site. Although most ecologists would be unwilling to accept this as a solution except in extreme cases, because of the importance of maintaining the original balance between species making up the community, if a species is destroyed by accident, there could at least be the possibility of returning it to its original site.

Many naturalists who are sympathetic to the aims of conservation wish to spread rare species at will throughout the British countryside. There are, however, strong arguments against introducing populations to new areas without very careful consideration of all the biological consequences. For example, there must be complete certainty that the species concerned is absent from the area to which it is intended to introduce it; the mixing of a native and introduced population can seriously affect any future genetic experiments. Introductions also affect work on the distribution patterns of species. At the Biological Records Centre efforts are being made to establish the native distributions of all the plants and animals which occur in the British Isles. To reduce the possibility of introductions giving misleading results it is essential that these are fully and accurately documented and the details sent to the Biological Records Centre.

Growing concern about uncontrolled introductions into the environment, particularly into nature reserves, stimulated the Conservation Liaison Committee of the SPNR to publish a booklet⁴ outlining criteria for introductions: three of the seven criteria referred to rare species. The booklet suggested that introduction is reasonable where a rare species has recently become extinct within a reserve area and the habitat is still suitable or could be modified to become so. Introductions may also be made where a species occurs in a habitat contiguous to or in the immediate vicinity of a reserve, but happens to be absent from the reserve itself. A species might also be moved to the safety of a nearby suitable reserve if its site is threatened in an unprotected area. It also recognized that it may be desirable occasionally to introduce rare species into areas outside their known geographical range for serious scientific experiment, on the understanding that the material can be removed if necessary at the termination of the experiment.

Action on a European Scale

Although the conservation of the British flora must be given high priority by English botanists, they should not restrict their concern too narrowly. Since European Conservation Year, concern for the protection of the world's biological riches has been widespread and transcended political and natural boundaries, so that British botanists can learn from conservation movements in other countries and also make their own contribution. Another reason for broadening botanical horizons is the experience of northern and western Europe in particular, where, on the whole, the standard of living is relatively high and where the enjoyment of natural history is a strong tradition with a wide amateur attraction. From these countries in recent years an enormously expanded tourist traffic has travelled south, particularly into the Mediterranean countries; here the richness and beauty of the flora attract many people, but the "development" they bring about is rapidly changing, and often irreparably damaging, that botanical richness. Nature conservation in southern Europe in particular is therefore urgently in need of planning and action—and inevitably much of the expert knowledge and resources to carry out these plans will have to come from the northern lands.

S. M. W. has started to use the international advisory structure for the publication of *Flora Europaea* to prepare a card index of the rare endemic vascular plants of Europe; this it is hoped can be relatively rapidly prepared and used to stimulate the appropriate authorities, through the conservation organizations. On a world scale, the preparation of a *Red Data Book* listing plants threatened with extinction has begun under the auspices of the International Union for the Conservation of Nature (the first list of Angiospermae has already appeared⁵); this will also provide many effective (if depressing) examples of the type of extinctions affecting the world's flora, examples which must be used to impress on governments and public alike the need for the creation of nature reserves and for other measures of nature conservation.

A third reason for publicizing the problems of flora conservation in Europe (and the whole world) is that the British tradition of gardening allied to interest in natural history, excellent as it is, has its dangers. Unfortunately many amateur naturalists apply less rigorous control of their collecting instincts outside Britain than at home. This is, of course, understandable when botanically little known, wild country is being explored, and we are not suggesting that basic "old-fashioned" collecting is inappropriate in every circumstance. It is, however, the case that many of the more conspicuous European plants are relatively rare and local, and indeed are often protected in the country concerned. It is incumbent on botanists to apply a conservation code of conduct in all circumstances, not just inside Britain, and in particular to take some trouble to find out whether there are conservation laws and protected areas in countries which they visit.

Rare plant species are often relicts surviving in restricted ecological niches. The opportunities for these species to spread to other, suitable habitats are minimal. Thus a site lost now is usually a site lost for ever. The challenge to the conservation movement is enormous: as well as flowering plants and ferns, other plants, such as bryophytes and lichens, are threatened and their rare species are equally in need of protection.

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Field Reversal or Self-Reversal?

by

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Correlations between the natural magnetic polarity and the oxidation state of magnetic minerals in certain rocks seem to conflict with the irrefutable case for ancient geomagnetic field reversals. This is a brief survey of the problem and its current status.

IN retrospect, the most surprising thing about Broun's discovery¹ of reversely magnetized rocks in southern India in 1855 was that it should have evoked so little surprise, especially in Broun himself. A comparable discovery today would quickly be presented at some international conference, whence it would reverberate around the world with the full force of the scientific grapevine. Broun was less excitable. It took him five years to publish what later turned out to be one of the most significant results in geophysics, though at the time he clearly had little idea of its importance.

In the event, Broun's work lay forgotten for over a century and thus made little impact. In the meantime, independent discoveries of reversely magnetized rocks began to find their way into the literature. Brunhes, who is generally credited with the first report², described a Quaternary lava flow which was not only reversely magnetized itself but which overlaid a reversely magnetized baked clay. Twenty years later, Mercanton³ provided similar evidence for reversals during the Tertiary and Permocarboniferous, and Matuyama⁴ discovered more reversed rocks in the Tertiary and Quaternary. Both Mercanton and Matuyama concluded that the Earth's magnetic field must have reversed its direction at least once in the past.

By the early 1950s it had become abundantly clear that these were not isolated instances but that at least a large minority of rocks were reversely magnetized. At this point an alternative to field reversal began to receive serious consideration. This was self-reversal, the possibility that some rocks possessed an intrinsic property whereby they could acquire a magnetization antiparallel to the ambient field, or whereby an originally parallel magnetization could reverse spontaneously. (As I understand it, Graham⁶ first took the possibility of self-reversal in rocks seriously, the idea coming from the work of Smith *et al.*⁷, who discovered self-reversal in a particular two phase iron-carbon alloy. Graham wrote to Néel, asking if he had any ideas on theoretical self-reversal mechanisms.) Theoretical self-reversal mechanisms were not difficult to find. Néel⁵ and Uyeda⁸ invented several mechanisms by which magnetostatic or exchange forces could produce self-reversals in magnetic systems with two interacting components. Verhoogen⁹ showed theoretically that natural impure magnetites may undergo magnetic self-reversal when cations migrate to preferred sites in the crystal lattice during a change from a disordered to an ordered state. Doubt about the reality of field reversals had set in; and the need to decide whether field reversal or self-reversal was the most likely became one of the principal preoccupations of palaeomagnetists.

From the palaeomagnetist's point of view, the problem with most self-reversal mechanisms is that they seem to be irreversible processes which leave behind no trace of their action (unless the

final reversely magnetized state is regarded as such). Nevertheless, there is a little experimental evidence for self-reversal in rocks. No sooner had Néel put forward his first theoretical self-reversal mechanisms than Nagata¹⁰ reported the now famous Haruna (Japan) dacite which self-reverses spontaneously and repeatably when cooled in a weak field from above 210° C. This remains the only known example of the self-reversal of total thermoremanent magnetization (TRM), although several cases of partial reversal have been discovered. A dacite pitchstone from Mount Asio (Japan)¹¹ and an iron sand from Sokoto (Japan)⁸ acquire a reversed TRM between 200° C and 300° C, but because it is small compared with that acquired parallel to the field in other temperature intervals, the total TRM is directed along the field. Other partial self-reversals have been detected in pyrrhotite-bearing rocks¹² and the Allard Lake ilmenite¹³, and inferred in a few other cases¹⁴.

In spite of these examples, the evidence is that total self-reversal is extremely rare. Pyrrhotite, for example, is not common in rocks and is certainly absent from most reversely magnetized rocks; and special heat treatments were necessary to induce self-reversal in the Allard Lake ilmenite. Moreover, the compositions of most of the rocks in which partial self-reversal has been detected are quite different from that of the basalts which feature so strongly in palaeomagnetic work. The evidence for field reversal, on the other hand, is now so overwhelming that there can be no doubt that almost all reversed rocks were produced during periods when the Earth's field was reversed. The tide began to turn in favour of field reversal when it became clear that about half of the world's rocks are reversely magnetized. This is just the proportion to be expected from field reversal because the dipole field, which according to the dynamo theory is governed by the Earth's rotation, is just as likely to align one way along the Earth's axis as the other. Self-reversal would produce this proportion only by coincidence.

But the case for field reversal is stronger than that. For one thing, almost all rocks baked by igneous bodies agree in polarity with the baking rock, irrespective of their compositions¹⁵. Self-reversal, on the other hand, would often produce baking and baked rock pairs of opposite polarity because the supposed self-reversal property is unlikely to be common to each member of a given pair. Furthermore, in cases where a wide variety of rock types in a single locality all possess reversed polarity, it is extremely unlikely that they all contain the self-reversing property. The really clinching evidence, however, is that all rocks of a given age, at least within the past four million years, have the same polarity irrespective of rock type, composition or location. For this reason it has been possible to construct a well defined polarity time scale covering the past four million years, correlate it with ocean magnetic anomaly patterns and use the correlation to determine seafloor spreading rates¹⁶. Self-reversal would have produced a random distribution of reversely magnetized rocks throughout this period. Lastly, in several cases where the rate of lava extrusion has been high enough, it has been possible to trace the variation in direction and intensity of the Earth's field as it changes from one polarity to the other¹⁷.

Correlations

Thus insofar as it is possible to prove any scientific theory, the reality of ancient geomagnetic field reversals has been

Table 1 Reported Differences between Normally and Reversely Magnetized Rocks in which the Oxidation States are Determined Petrographically

Rocks	IEFR	Difference between Normally (N) and Reversely (R) Magnetized Samples
(1) Carboniferous lava flows, Kinghorn, Scotland ²⁵	Yes	On average R samples contain about seven times as much separate ilmenite* as N samples.
(2) Tertiary lava flows, Cape Kawajiri, Japan ²⁵	No	On average R samples contain about twice as much separate ilmenite* and about three times as much titanomagnetite* with ilmenite lamellae as N samples, but only about one third as much optically homogeneous titanomagnetite*.
(3) Quaternary and Tertiary lava flows, Iceland ²⁵	No	Same trends as in (2) but N and R differences not statistically significant unless taken in conjunction with (1) and (2).
(4) Tertiary lava flows, Columbia Plateau, USA ²⁶	Yes	Titanomagnetites in R samples more highly oxidized (statistically) than in N samples.
(5) Tertiary lava flows, Mull, Scotland ²⁷	No	As (4).
(6) Tertiary lava flows and dykes, Iceland ²⁸	Yes	As (4) in spite of the fact that although each lava flow possesses only one polarity, a wide range of oxidation states existed in most of them. No correlation between dyke polarities and oxidation states.
(7) Tertiary dykes, Mull, Scotland ²⁹	No	The higher states of titanomagnetite deuteric oxidation and higher separate ilmenite* content are associated with reversed polarity.

IEFR, Independent evidence of field reversal

* Measured as a proportion of total opaque mineral area.

established*. It is implicit in such a field reversal system that all rocks of a given age should possess the same polarity as long as self-reversals do not occur also, or occur very infrequently. It is also implicit that the polarity of any rock is completely independent of any of its physical, chemical or petrographic properties. The only exception to this is, of course, the field defining property—that the rock should acquire a magnetization in the direction of the ambient field at the time of acquisition; and as far as it is possible to tell from laboratory experiment this condition is fulfilled (except for the Haruna dacite) irrespective of the nature of the minerals present. The lack of a correlation between a rock's polarity and other properties, on the other hand, does not necessarily rule out self-reversal because the self-reversal mechanism may be intrinsically undetectable or at least so subtle that it has not yet been detected. Conversely, the presence of such a correlation would positively support self-reversal.

What then are we to make of the correlations between polarity and other properties which have been observed in several sets of rocks? Differences in petrographic texture, grain size and the form of olivine grains have been observed between normal and reversed German basalts¹⁸; excess TiO₂ has been discovered in reversed basalts from southern Siberia¹⁹; the Fe₂O₃/FeO ratio is greater in some reversed Armenian Quaternary lavas than in the corresponding normal ones²⁰; and reversed lavas from Kazakhstan (USSR)²¹ and reversed metamorphic rocks from the Adirondack mountains (USA)²² are more highly oxidized than the respective normal samples. The fact is that, rightly or wrongly, proponents of field reversal have tended to dismiss these and a few other examples as insignificant on the grounds that there are so few of them and that the properties correlating with polarity are too varied to enable generalizations to be made. (Most of them, however, seem to imply higher oxidation states for reversed rocks.) They were interesting examples which hopefully could be put down to coincidence or local conditions, or which were, at worst, isolated cases of possible (but unproven) self-reversal that did nothing to disprove the predominance of field reversal.

But during the past few years the number of well documented correlations has shown an embarrassing increase, so that it is no longer possible to dismiss this type of evidence so lightly. In principle, these more recently discovered correlations do not differ from many of those which preceded them. The reason why they are perhaps more significant is that more

* I have in mind here, of course, Popper's view that it is not possible to prove a valid theory but only to disprove an incorrect one. I do not wish to labour this point because of the wealth of evidence in favour of field reversal; but in view of what follows it might be wise to keep the options open for the time being.

sophisticated petrographic techniques have been developed for the objective assessment of oxidation states, and these have been applied systematically to large collections of rocks.

The results of these studies are shown in Table 1. In all the reported correlations, reversed samples are more highly oxidized on average than normal samples, the most important measure of oxidation being the deuteric oxidation state of the titanomagnetites. The nature of the conflict between field reversal and self-reversal is best illustrated by reference to the Columbia Plateau basalts. In this study the opaque titanomagnetite grains were divided into five classes depending on their state of oxidation—ranging from class 1 (optically homogeneous titanomagnetites: lowest oxidation state) to class 5 (two or three phase grains containing pseudobrookite, hematite and rutile: highest oxidation state). Each rock sample was then placed into one of these classes corresponding to the predominant grain type. This procedure is open to the obvious objection that it lacks objectivity. For this reason Wilson, Haggerty and Watkins²³ later developed a more rigid technique for petrographic analysis. However, Watkins and Haggerty²⁴ have shown that the correlations are clear irrespective of the degree of sophistication of the technique.)

The strength of the correlation between oxidation state and polarity in these rocks (Fig. 1) is startling, not least because the Columbia Plateau basalts yield independent evidence (baked-baking pairs of the same polarity) that the reversed samples are due to field reversal. Furthermore, the samples investigated included a well documented polarity transition zone; and the correlation holds right across this zone. That there is a polarity-oxidation correlation is undeniable, though it is not a one to one but a statistical correlation. And unless the field reversal evidence has been totally misinterpreted, it is equally undeniable that the reversely magnetized rocks are due to field reversal.

Possible Explanations

The dilemma posed by these correlations is clear. For a start, we must assume that either field reversal or self-reversal is the predominant process, for if both effects are common there would presumably be little order at all—that is to say, there would be neither petrography-polarity correlations nor convincing evidence for field reversal. But which is the dominant process? General experience together with the particular evidence from baked contacts suggests field reversal; the polarity-oxidation correlations suggest self-reversal. Or is there some other way of reconciling the conflicting evidence?

There seem to be just three options. The first is that the correlations are merely fortuitous³⁰—and thus field reversal

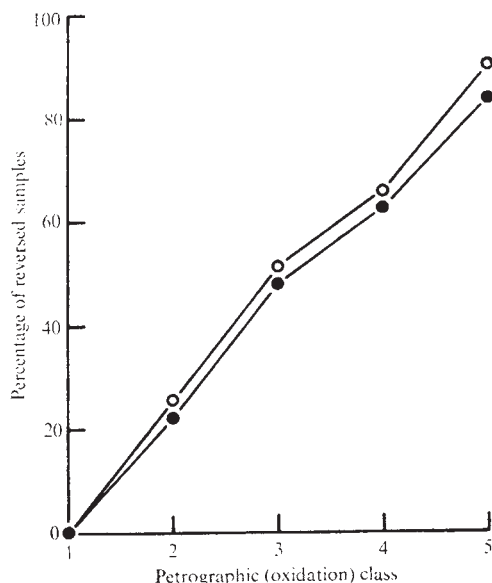


Fig. 1 The polarity-petrography (oxidation) correlation in Columbia Plateau basalts. Open points are for normal and reversed samples from ten different sites. Closed points are for a single section containing transition zone. (After Wilson and Watkins²⁶.)

is not invalidated. We can visualize several possible causes of "accidents"—unrepresentative sampling, the incorrect determination of polarities due to the presence of secondary magnetic components, and lack of significance in the number of correlations. But none seems likely to explain all the facts. All the samples listed in Table 1 were carefully "cleaned" magnetically, and so there can be no doubt that the determined polarities are correct. The effects of biased sampling are more difficult to detect, but it is significant that correlations are always in the same sense—high oxidation states are associated with reversed samples. Sampling errors alone would presumably produce fortuitous correlations, if at all, in both senses. The same argument can be applied to the question of significance. It may be true that so far the number of correlations is small compared with the total number of rock sets in the world; but surely if these correlations were fortuitous, some would be in the opposite sense. Nevertheless, it is fair to say that the small number of correlations does pose a question of confidence. Only time will tell whether many, or most, rock sets show correlations.

The second possibility is that field reversal has not occurred, and thus that the reversely magnetized rocks are due to self-reversal. But the independent evidence for field reversal in some of the rock sets showing polarity-oxidation correlations, and the evidence for field reversals in general, is just too strong to be denied at this stage.

The third explanation, which at first seems as unlikely as the other two, is that field reversal is the cause of the reversely magnetized rocks, but that the observed correlations are nevertheless real and significant. This must mean that there is a statistical correlation between the polarity of the geomagnetic field which originates in the core and the oxidation state of the lava flows which originate in the upper mantle. Incredible though this may seem, circumstances dictate that some serious thinking is done along these lines.

Little thought has been devoted to interactions between mantle and core processes. Hide and Malin³¹, however, have demonstrated a significant correlation between the Earth's gravitational field and the non-dipole geomagnetic field. After a previous suggestion by Hide³², this correlation is attributed to undulations of the core-mantle interface a few kilometres in amplitude, which would interact strongly with fluid motions in the core. Because only minor variations in core motions are required to reverse the sign of the dipole field, and because core-mantle interface undulations are

likely to be affected by motions in the lower mantle, Hide³³ has suggested that "it would not be surprising to find that 'reversals' are correlated to some extent with other phenomena that may be affected by motions in the mantle, such as tectonic activity (mountain building, ocean-floor spreading, continental drift and so forth). . . . The search for such correlations might therefore lead to results of direct theoretical importance".

It is not yet clear whether or not this is a lead towards the understanding of polarity-oxidation correlations. The oxidation state of a lava is probably governed by the availability of water³⁴; and this means that the connexion between core processes and lava composition presents a more subtle problem than that between, say, core processes and tectonic activity. The solution will thus be that much more difficult. In the meantime, the field is wide open to other explanations.

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The Statistics of Crowd Fluids

by

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The speed/velocity distribution functions have been measured for three crowd fluids in the gaseous phase. Good agreement is obtained with Maxwell-Boltzmann theory except for a significant deviation near the frequency mode of each distribution. This is attributed to sexual inhomogeneity.

It often seems that there are random fluctuations in the movements of people in large crowds, especially if the people are not too closely packed together. Yet each person has mass and velocity, which suggests that classical Maxwell-Boltzmann statistics might describe the motion of a crowd of people. What follows is a development of this idea, which is tested by measurements obtained from real crowds.

Suppose there is a passageway which is long compared with its width and along which people are moving, more or less in the same direction. Individuals will be either standing still, walking or running, and these activities are defined as the energy modes of the crowd. The particle density will be defined as the number of persons per unit area and—at least if this quantity is small—it will be assumed that each individual will be able to move at some chosen characteristic speed. At one end of the passage, the crowd may be forced to slow down, probably by the need to surrender a ticket at a barrier, when it may be expected that people will bunch into a densely packed crowd which moves along with a slow elbow-to-elbow shuffle. This transition will be called a phase transformation—the loosely packed phase is a crowd gas and the densely packed phase is a crowd liquid. The Maxwell-Boltzmann theory is applied only to the gaseous phase.

The analysis can be simplified by a number of assumptions. First, movement is supposed to take place on a continuous surface and to be defined at any time t by the position (x, y) and velocity (V_x, V_y) , say, of all the N individuals in the crowd. Further, if the crowd is homogeneous, each particle in it will have the same mass and the same probability of velocity components in a given mode. (The concept of homogeneity is analogous to the concept of chemical purity in molecular systems.) A particle is said to be composite if it consists of two or more persons, and prime if it consists of only one person. Composite particles are attributed to the existence of social bonds among the people which cause some of them to walk in pairs or larger groups, to run together or otherwise to associate in groups.

It is assumed that irrespective of whether the particles are composite or prime, they are statistically independent of each other in position and velocity coordinates. The velocity of any particle is also assumed to be uncorrelated with its position. Finally, it is assumed that the crowd is in equilibrium, and that its average properties can be obtained from consideration of stationary ergodic processes. In particular, the crowd itself—a homogeneous collection of prime particles in equilibrium—may be treated as the statistical ensemble of any individual. Its average properties could therefore be found by measuring for a sufficient time the ensemble averages of all the people at the same instant, or the phase averages of only a few people, or indeed of only one person.

Equations may be obtained from the Maxwell-Boltzmann theory of a homogeneous crowd gas composed of statistically independent particles in equilibrium on a two-dimensional continuous surface (with the particles uncorrelated with their position in the system). The probability density function, $P(V_x)$, for a single fluctuating velocity component, V_x , is

$$P(V_x) \equiv \frac{1}{N} \frac{dN_{V_x}}{dV_x} = \frac{1}{\sqrt{2\pi} v_{r.m.s.}} \exp\left(-\frac{1}{2} \frac{V_x^2}{v_{r.m.s.}^2}\right) \quad (1)$$

where $v_{r.m.s.}$ is the root-mean-square of the speed $v \equiv |V|$. This may be combined with a similar expression for V_y , to give the velocity resultant, V

$$P(V) \equiv \frac{1}{N} \frac{dN_V}{dV} = \frac{1}{2\pi v_{r.m.s.}^2} \exp\left(-\frac{1}{2} \frac{V^2}{v_{r.m.s.}^2}\right) \quad (2)$$

The probability density function for the speed is

$$P(|V|) \equiv \frac{1}{N} \frac{dN_v}{dv} = \frac{\pi v^2}{4 v_{r.m.s.}^2} \exp\left(-\frac{\pi v^2}{4 v_{r.m.s.}^2}\right) \quad (3)$$

where for convenience this result has been expressed in terms of the mean speed $\bar{v} = \sqrt{\pi/2} v_{r.m.s.}$ of the fluctuations. There is sometimes a mean translational motion or flux superimposed on the fluctuating part of the motion, for example, a crowd moving along a passageway or one which is otherwise confined to some type of channel. Equation (1) must be rewritten in these circumstances so that it is still valid for the fluctuating component $V'_x \equiv V_x - \bar{V}_x$:

$$P(V'_x) \equiv \frac{1}{N} \frac{dN_{V'_x}}{dV'_x} = \frac{1}{\sqrt{2\pi} v_{r.m.s.}} \exp\left(-\frac{1}{2} \frac{V'^2_x}{v_{r.m.s.}^2}\right) \quad (4)$$

where V_x is the component of the mean velocity of translation or flux. Equations (2) and (3) must be treated in a similar manner.

Real Crowd Measurements

Several crowds in the city of Sydney were examined in an attempt to find some which were approximately homogeneous, and had a sufficiently small particle density to ensure that most individuals would be statistically independent and in the gaseous phase. Three crowds which appeared to have the desired properties were eventually selected.

Students. A crowd of university students on a footpath outside the Fisher Library at the University of Sydney was examined and the distribution of the velocity component, V_x , parallel to the footpath measured for the walk mode only. It was considered that data on about 700 students would constitute a comparatively accurate test of the theory for a single mode. The crowd was more or less confined to a channel, the footpath, and it had a definite translational flux towards and away from the library; equation (4) is therefore appropriate. Counts were only taken of those students moving away from the library and the measured distribution is compared with the Maxwell-Boltzmann distribution (obtained from equation (4)) in Fig. 1. The agreement between the two curves is seen to be reasonably good.

Pedestrians. The progress of a crowd of adults of all ages using a pedestrian crossing in a busy city street at Circular Quay, Sydney, was influenced by the presence of motor vehicles. Only 9 people out of 637 studied were found to be running and none at all were standing on the crossing, and

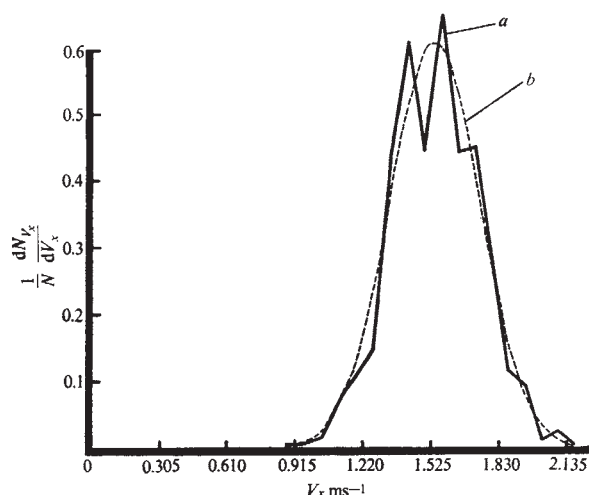


Fig. 1 Probability density function of the velocity component V_x distribution of 693 students in walk mode on a footpath outside Fisher Library, University of Sydney. Curve a , measured distribution; curve b , Maxwell-Boltzmann distribution. $V_x = 1.53 \text{ m s}^{-1}$; $v_{r.m.s.} = 0.201 \text{ m s}^{-1}$.

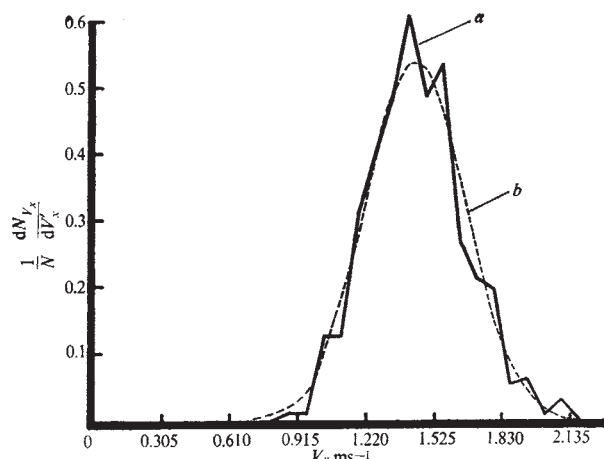


Fig. 2 Probability density function of the velocity component V_x distribution of 628 pedestrians in walk mode on a zebra crossing at Circular Quay, Sydney. Curve a , measured distribution; curve b , Maxwell-Boltzmann distribution. $V_x = 1.44 \text{ m s}^{-1}$; $v_{r.m.s.} = 0.228 \text{ m s}^{-1}$.

only enough data were obtained to test the walk mode distribution. This crowd was also confined to a channel so equation (4) is again appropriate. No account was taken of the direction in which the people crossed the road, and in fact the selection rules for this crowd were generally less restrictive than for the students. In spite of this the agreement with the theory as shown in Fig. 2 is, if anything, better than for the students.

Children. A direct test of equation (3) for more than one mode required a crowd with no translational flux, and children in a school playground appeared to have this property. Because of the possibility that the homogeneity of this crowd would be more dependent than in other cases on the ages of the individuals present, an effort was made to select the children from as narrow an age group as possible. The part of the playground allotted to 6–8 year old children of the Infants Department of Glebe Primary School, Sydney, was therefore selected for study. All three modes were found, and the measured speed distribution across all the modes is shown in Fig. 3. These data have been resolved into its components in Fig. 4, and also compared with the Maxwell-Boltzmann theory (equation (3)).

Males and Females

Males and females were present in all the crowds and no distinction was made on the basis of sex because it was con-

sidered that for each case the uniformity of activity and environment together with attention paid to the selection of the ages of the individuals (where it appeared to be relevant) would produce approximately homogeneous crowds for study. Agreement with the Maxwell-Boltzmann theory is generally satisfactory except near the maximum or frequency mode of each distribution. Statistical tests which included chi-squared tests and acceptance-rejection tests (Abramowitz and Stegun¹) showed that there was probably an assignable cause for the difference between the theory and measurement. The results of the chi-squared tests, based on the Maxwell-Boltzmann hypothesis, are summarized in Table 1. The level of significance is obviously altered considerably if the two or three class intervals responsible for most of the deviation are left out of the tests and the results of depleting the data in this way are also shown in Table 1. The acceptance-rejection tests were designed to select the same sample sizes from the Maxwell-Boltzmann population as had been obtained by observation. This introduced sampling fluctuations into the theoretical data and provided a better basis for comparison with the measurement. About 100 Maxwell-Boltzmann samples were obtained by computer for each distribution and the mean, μ , and standard deviation, σ , of the sample curves for each class interval were then computed. On the assumption that the Maxwell-Boltzmann sample fluctuations were normally distributed it was found that the acceptance-rejection tests confirmed the chi-squared tests because the measured curves were either inside, or just outside, the $\mu \pm 2\sigma$ (95.4%) band, and within the $\mu \pm \sigma$ (68.3%) band, for the depleted data. An example of an acceptance-rejection distribution is shown in Fig. 5.

The deviation from the Maxwell-Boltzmann curves is

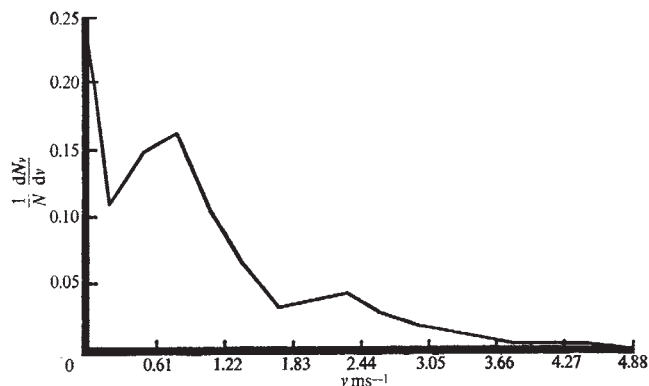


Fig. 3 Probability density function of the total speed v distribution for 779 children aged 6–8 years in a school playground at Glebe, Sydney.

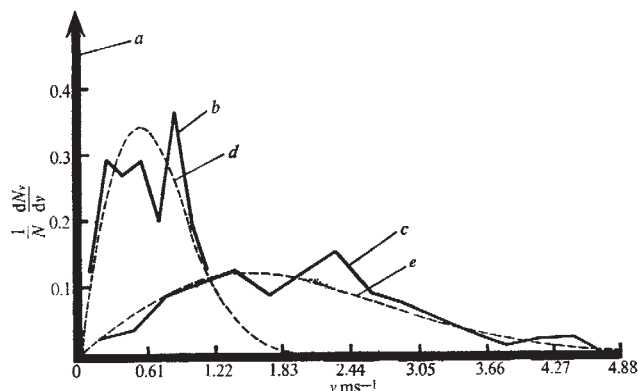


Fig. 4 Resolution into component energy modes of probability density function for speed v distribution for 779 children. Curve a , still mode (185); curve b , walk mode (377); curve c , run mode (217); curves d and e , Maxwell-Boltzmann. For walk mode, $v = 0.673 \text{ m s}^{-1}$; for run mode, $v = 1.91 \text{ m s}^{-1}$.

roughly an M-shape, and near the maximum for all the distributions in Figs. 1, 2 and 4. The most natural explanation is that each crowd consists of a mixture of two populations whose distributions are displaced from one another. The two populations are probably males and females, and male students, for example, have a larger V_x than female students, so that the two means correspond to the two peaks in the measured distribution (Fig. 1). The pedestrians display a similar distribution separation and, in the case of the children, the male and female peaks correspond to the frequency modes of each separate distribution. There is obviously an inhomogeneity in any crowd due to sexual differences.

The deviation was unfortunately not anticipated during the planning of the observations. Homogeneous crowds were selected on the basis of the uniformity of environment and activity, and the ages of the individuals were appropriate. The criteria of gaseous phase and statistical independence were satisfied by selecting crowds of small particle density. It was planned to count all prime particles as they appeared, but with

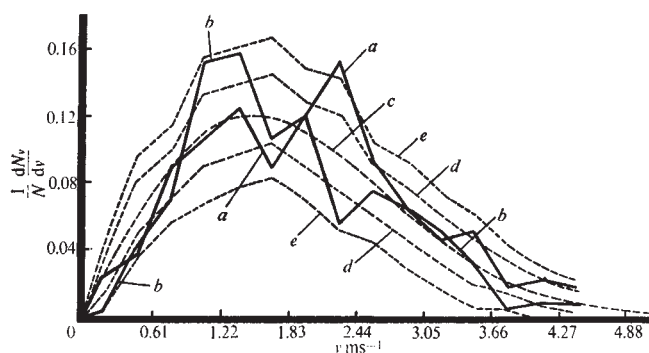


Fig. 5 Probability density function of speed v distribution of 217 children in run mode. Comparison of measured curve a with typical computer generated curve b , Curve c , Maxwell-Boltzmann; curve d , one standard deviation from the mean or the computer generated curve; curve e , two standard deviations from the mean.

Table 1 Summary of Chi-squared Tests on Maxwell-Boltzmann Hypothesis

	Students Walk mode	Pedestrians Walk mode	Children Walk mode	Children Run mode
χ^2 (d. of f.)	20 (11)	17 (13)	24 (9)	13 (10)
% significance	95	75	99.4	75
χ^2 (d. of f.)	8.8 (8)	11 (10)	7.4 (7)	6.5 (9)
% significance	60	65	60	50

the benefit of hindsight males and females would be considered as different populations. Only fragment information on the effect survives in the data and a complete reassessment is not feasible.

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Indo-Australian Stratigraphy and the Configuration and Dispersal of Gondwanaland

by

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India and Australia are reassembled in Gondwanaland from stratigraphic evidence with their northern margins facing Tethys and their southern margins within the interior. A similar reconstruction of all Gondwanaland entails insignificant reorientation of constituent continents, and is consistent with a pattern of continental dispersal indicated by the gross geology of the Indian Ocean.

ANALYSIS of the gross stratigraphy of western Australia and India (Figs. 1 and 2) reveals parallel facies trends from Permian, Triassic and Jurassic dominantly non-marine sequences in the south (Perth Basin of south-west Australia, Gondwana series of peninsular India) to fairly complete Phanerozoic wholly marine sequences in the north (north-west Australia, Himalayan India). We infer from this that before the breakup of Gondwanaland, south-west Australia and peninsular India lay within the interior, and north-west Australia and Himalayan India along its margin. This inference is confirmed by the youthful rifted character of the continental margin of south-west Australia (Fig. 2b). In Fig. 2a we present a reconstruction

of Australia and India in Gondwanaland that is consistent with their gross stratigraphy and structure. The Perth Basin, with its predominance of non-marine Permian to Jurassic sediments equivalent in age to marine sediments in the other more northerly basins, and the Gondwana series of peninsular India, lie deep in Gondwanaland. The Carnarvon Basin faces a Tethyan gulf and the Canning Basin, Bonaparte Gulf Basin, Timor, and Himalayan India face Tethys. This reconstruction differs from those of earlier authors who favoured an Indo-Australian connexion¹⁻⁴ because it places only south-west Australia against eastern peninsular India.

The stratigraphy and structure of India and Australia are readily explained in terms of a sequence of rifting, rupture, and drift. The almost complete absence of Late Carboniferous sediments in Western Australia records the arching that preceded the deep rifting of the Permian (Fig. 3a). Rifting in the epicontinental Canning and Bonaparte Gulf Basins ceased at the end of the Permian, but it persisted in the intracontinental Perth and Carnarvon Basins. The Perth Basin rifting was renewed during the Middle and Late Triassic with the deposition of coarse arkosic piedmont sandstones and red beds⁵, and, possibly during the entire Jurassic, part of the Carnarvon Basin subsided rapidly to accumulate the thick deep-marine Dingo claystone.

India and Australia ruptured in the latest Jurassic or earliest Cretaceous with the extrusion of the Rajmahal⁶, Bunbury^{7,8} and Ashmore Reef⁹ basalts and probable tuff in the Broome

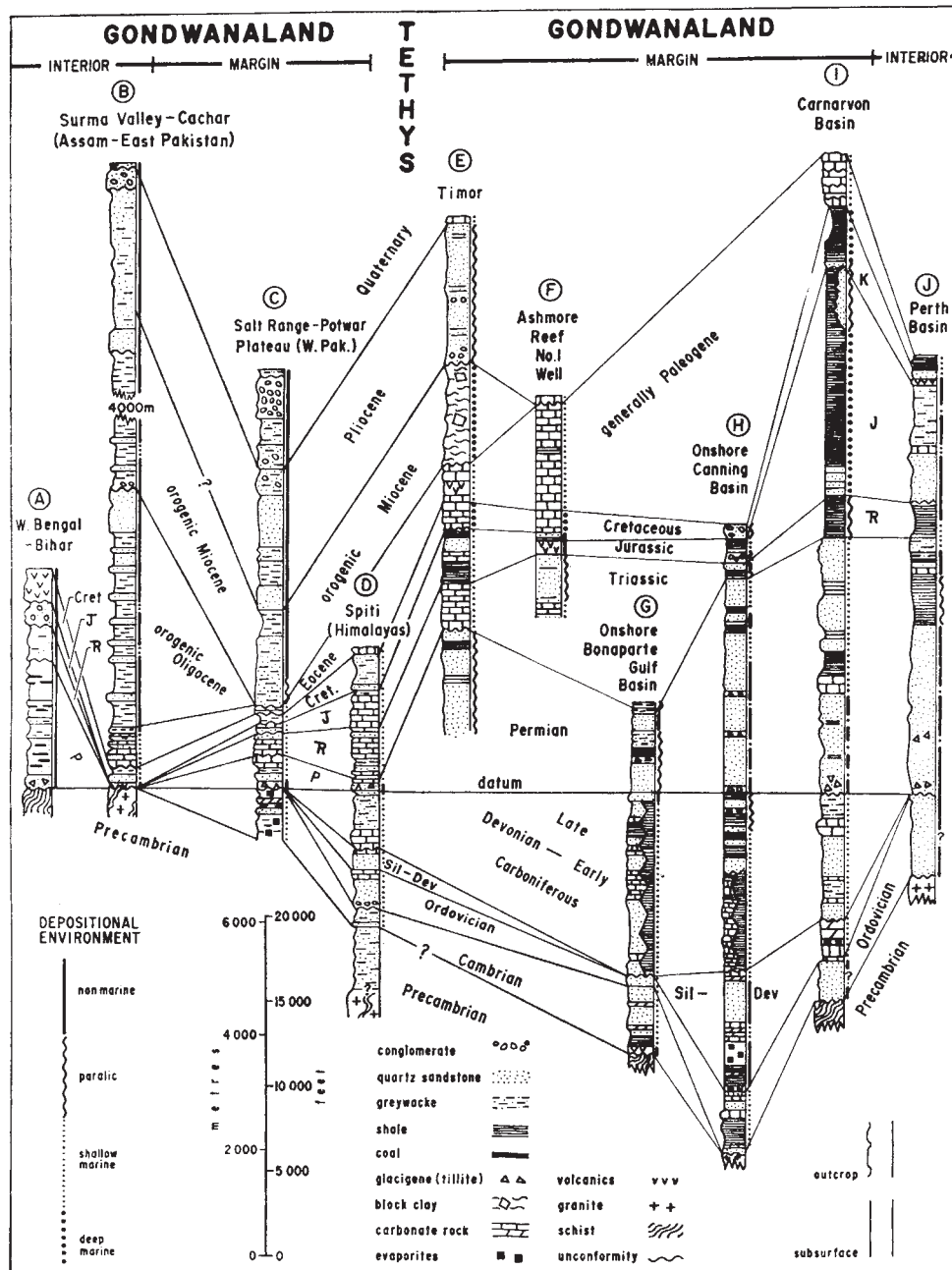


Fig. 1 Stratigraphic columns of selected areas shown in Fig. 2a. Datum is base of Permian. Sources are Pascoe³⁸ (India), Evans^{35,39} (Assam), Audley-Charles⁴⁰ (Timor), Veevers^{9,41} (Timor, Ashmore Reef, onshore Bonaparte Gulf and Canning Basins), Condon³⁶ (Carnarvon Basin), Johnstone and Willmott³⁷ and McWhae *et al.*⁷ (Perth Basin).

A, The Bihar Basin of West Bengal exemplifies the Permian to Early Cretaceous Gondwana system of India and East Pakistan. Preserved in rifts in the Pre-Cambrian basement, this system comprises non-marine sediments with minor Early Permian and Early Cretaceous marine intercalations. A Sakmarian intercalation in the Umaria Coalfield of central India contains an invertebrate fauna like that of the Carnarvon Basin and the Salt Ranges. Similar intercalations have been recently discovered in northern India⁴². Extensive flows of the Rajmahal Basalt⁶ were erupted in the Neocomian.

B, In Assam, Eocene transgressive sediments overlap Early Cretaceous sediments and equivalents of the Rajmahal Basalt^{43,44}. This transgression started earlier, in the Albian, in eastern peninsular India⁴⁵. Just before the close of the Eocene, the sea withdrew except for a few minor transgressions⁴⁶ in a definitive regression that extended over the entire northern part of the Indian block. Deposition of thick molasse followed in the Oligocene in Assam⁴⁷, but elsewhere the oldest molasse is Late Miocene.

C, The sequence in the Salt Range bridges, the non-marine Permian and Mesozoic Gondwana system, and the marine Palaeozoic and Mesozoic Himalayan sequence. The youthful age (Miocene) of the molasse should be noted.

D, The Spiti sequence exemplifies the almost unbroken Palaeozoic-Mesozoic deposition of shallow marine sediments at the Tethyan margin.

E, Timor occupies the north-west edge of the Australian block⁹, and its oldest dated rocks are autochthonous Early Permian paralic sediments similar to age equivalents in Western Australia. The Mesozoic sequence comprises shallow marine sediments except an Albian deep-water radiolarite. Permian reef limestone (not shown), presumably originally deposited at the more northerly extreme

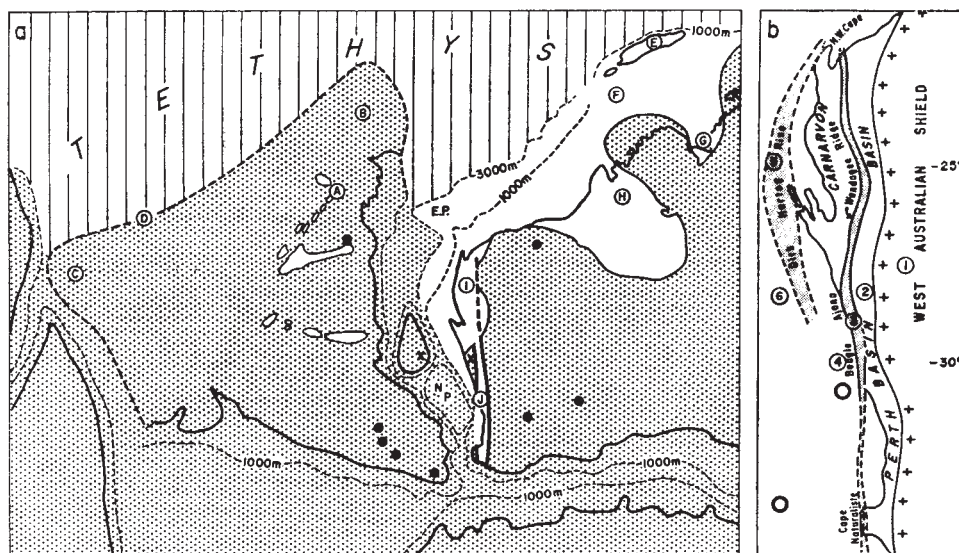


Fig. 2 *a*, Reassembly of Australia and India in Gondwanaland. Phanerozoic basins of Western Australia and Gondwana system of peninsular India are left blank. A to J mark the locations of the stratigraphic columns in Fig. 1. Positions of parts of Africa and Antarctica are from Fig. 4. Assam is regarded as part of the Indian block, as indicated by the connexion of the Shillong Hills of Assam to peninsular India by the subsurface Pre-Cambrian Rangpur Ridge and Bogra-Jajalgar Coalfield (Gondwana system) of East Pakistan^{34,35}. Continental margins are delineated by 1,000 m isobath except margins of north-west Australia and Naturaliste Plateau, delineated by 3,000 m isobath. Timor Trough is omitted. Naturaliste Plateau may be regarded as detached or connected but rotated. Solid circles mark locations of the oldest dated rocks (>3,000 million years) on the Indian and Australian continents, and crosses mark locations of amphibolite/granulite facies rocks of age 1,100 million years (ref. 1). EP, Exmouth Plateau; NP, Naturaliste Plateau. *b*, Structure of south-west Australia^{36,37}. Open circles mark locations of Late Cretaceous cores^{11,12}. North-south lineaments die out just north of North West Cape.

Beds¹⁰ (Fig. 3b). Deposition of Late Cretaceous deep-sea sediment along the length of Western Australia (Fig. 3c), notably at places^{11,12} which previously lay deep within Gondwanaland, marked the final separation of Australia and India.

Collision of the detached Indian and Australian blocks with Asia was marked by regression, thrusting, orogeny, and subsequent molasse deposition. The north-east part of the Indian block collided with Asia at the end of the Eocene as shown by regression and the first deposition of molasse in Assam. Australia separated from Antarctica in the Eocene (J. J. V., to be published) and collided with Asia in the Middle Miocene, as suggested by thrusting and the emplacement of block clay (argille scagliose) on Timor, broad folding of the floor of the Timor Sea¹³, and deposition of Pliocene molasse in Timor.

Almost all the many geologists who have followed du Toit¹⁴ with reconstructions of Gondwanaland have accepted the long postulated match of the Atlantic margins of Africa and South America and most have placed southern Australia against the Wilkes Land sector of east Antarctica as he did. The morpho-

logical analyses of Carey¹⁵, Sproll and Dietz¹⁶, and Smith and Hallam¹⁷ have confirmed and refined du Toit's Afro-American and Austral-Antarctic matches; the principal pieces of the Gondwanaland jigsaw are thus reduced from five to three, namely Africa/South America, Australia/Antarctica, and India.

We doubt whether morphological analysis can provide a unique reassembly of these three remaining units. The Afro-American and Austral-Antarctic matches are made across oceans with a simple median ridge and free of continental fragments (microcontinents), but reassembly of Africa/South America, Australia/Antarctica, and India must be made across an ocean of complex morphology littered with proven and probable continental debris. Our postulated connexion between Australia and India (Fig. 2a) reduces the problem of Gondwanaland reassembly to the relative placement of Africa/South America and India/Australia/Antarctica. Our solution is shown in Fig. 4.

Smith and Hallam¹⁷ reject a reassembly of this kind because "with India in this position . . . India/Australia/Antarctica cannot be fitted against Africa without leaving large gaps

margin of Tethys, was thrust onto Timor during the Middle Miocene, and was followed by emplacement of block clay and deposition of molasse.

F, The Ashmore Reef sequence, drilled no deeper than Upper Triassic, is noteworthy for its Jurassic/Cretaceous basalt and Late Cretaceous deep-sea ooze.

G, The onshore Bonaparte Gulf Basin has a fairly complete dominantly marine Palaeozoic sequence complemented offshore by the fairly complete dominantly marine Mesozoic and Cenozoic sequence of Ashmore Reef.

H, The onshore Canning Basin likewise contains a fairly complete dominantly marine Palaeozoic sequence, but with non-marine intervals in the Silurian/Devonian and Permian.

I, The Carnarvon Basin contains dominantly shallow marine Late Silurian and younger sediments. The thick deeper-marine Jurassic Dingo claystone is noteworthy.

J, The Perth Basin differs radically from the other basins in lacking older Palaeozoic sediments other than the presumably non-marine Early Palaeozoic Tumblagooda sandstone, and in its main Permian to Jurassic sequence being dominantly non-marine. South of Perth, the sequence is wholly non-marine (J. J. V., to be published). Marine intercalations of Early Permian⁷, Early Triassic⁴⁸, and Middle Jurassic⁶ ages in the northern Perth Basin are minor, and parts of the Permian marine intercalations were probably deposited under conditions of restricted circulation in a barred basin⁴⁹.

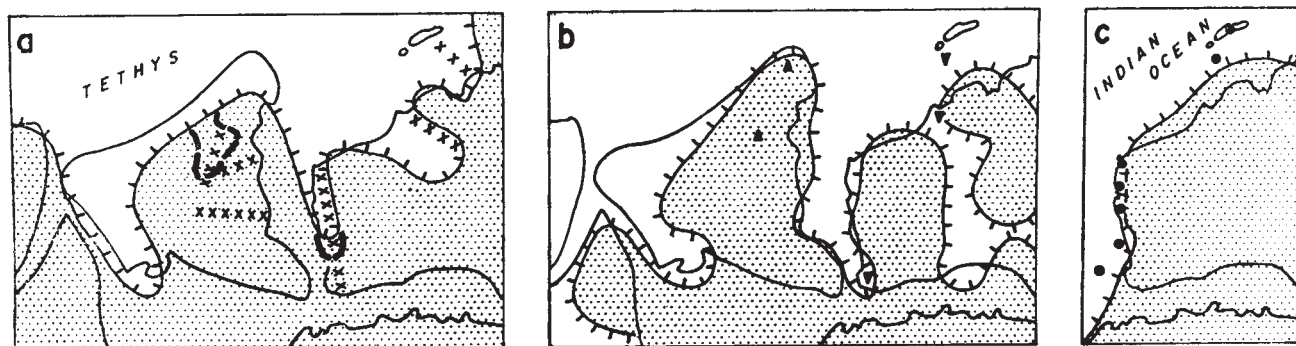


Fig. 3 Palaeogeographic maps. Positions of continents indicated by present coastlines. *a*, Permian. Hachured line shows shorelines, and broken line extent of intermittent marine incursions. Crosses show thick sediments in rifts. *b*, Late Jurassic/Early Cretaceous. Solid triangles indicate volcanics. *c*, Late Cretaceous. Solid circles show deep-sea sediments.

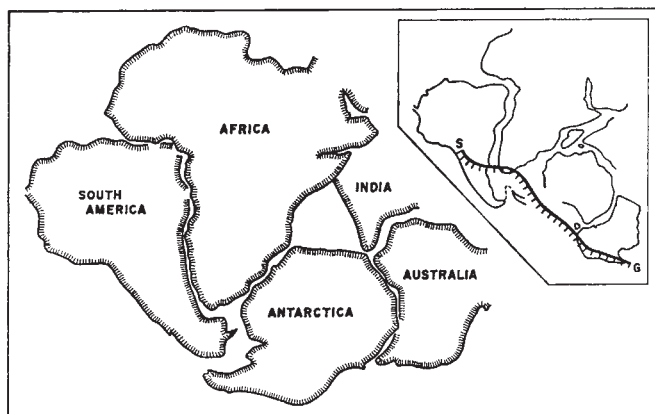


Fig. 4 Configuration of Gondwanaland. Internal triangular gap accommodates Madagascar and other microcontinents. Continental outlines at 500 fathom contour from Smith and Hallam¹⁷. Inset: du Toit's reconstruction of Gondwanaland, using sea level outlines (S-G, Samfrau Geosyncline).

between them". Yet the triangular space between India, Africa and Antarctica in our reconstruction provides an adequate area in an appropriate place for Madagascar and for the other numerous microcontinents of the Indian Ocean^{18,19} for which other reconstructions make no provision.

The recent morphological analyses of Smith and Hallam¹⁷ and Sproll and Dietz²⁰ support du Toit's relative placement of Africa and Antarctica (Fig. 4, inset) which differs substantially from our own. We do not, however, accept such analyses as necessarily conclusive, limited as they may be by sparse bathymetric data and by the inevitable predispositions of the investigator. The matching of relatively short sections of continental margin is achieved in this instance at the expense of the gross morphological congruence of Gondwanaland; it entails substantial overlap of the continental shelves of the Antarctic peninsula, Africa and South America, and substantial underlap between Africa and Australia/Antarctica—a yawning gap which India and the microcontinents of the Indian Ocean would fill most inadequately. The Antarctic peninsula overlap can be attributed to post-Gondwanaland changes in the morphology of Antarctica^{15,20}, but no such explanation can account for the complementary underlap. Both the eastern margin of Africa and the western margin of Australia appear to be rifts along which Gondwanaland disintegrated, and must therefore have lain adjacent to other portions of Gondwanaland before drifting occurred. Du Toit's Afro-Antarctic placement makes this requirement impossible to fulfil (compare Fig. 4 and inset).

The rupture and dispersal of a supercontinent necessarily involve the creation of new oceanic areas bounded by new continental margins, and these can be expected to yield vital information on the pattern and timing of dispersal. Fig. 5

presents our understanding of the gross geology of the Indian Ocean which—for the seafloor—is based chiefly on the work of Heezen and Tharp²¹, Le Pichon and Heirtzler²², and Heirtzler *et al.*²³. Interpretation of its magnetic anomaly pattern^{22,23} indicates that about half the area of the Indian Ocean was generated during the Cenozoic by spreading along the axis of the segmented north-west-south-east ridge system, commencing in latest Cretaceous (67 million years) in the north-west sector and in Late Eocene (43 million years) in the south-east. The Cenozoic age of this strip of seafloor and the timing of the onset of spreading are confirmed by the geology of the adjacent continental margins. The Deccan Traps which cover half the

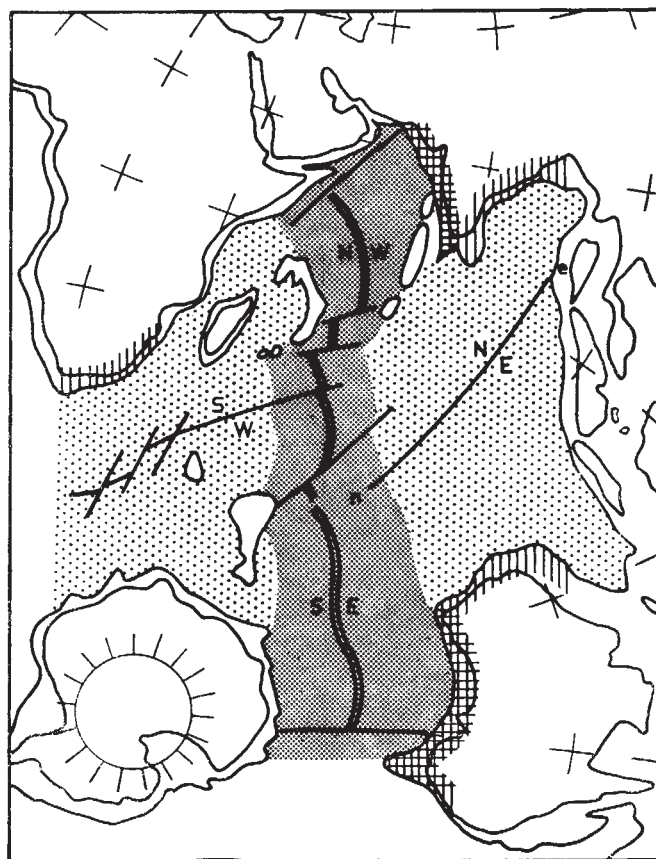


Fig. 5 Gross geology of Indian Ocean. Continents, delineated by 2,000 m depth contour, unshaded: light ornament, continental margins initiated in Cretaceous; heavy ornament, continental margins initiated in Cenozoic. Ocean floor shaded: light tone, Cretaceous seafloor; dark tone, Cenozoic seafloor; single lines, faults; double lines, actively spreading ridge system. NE, NW, SE, SW, denote geographic sectors of Indian Ocean. n-e denotes Ninetyeast Ridge. Oblique mercator projection, after Carey³.

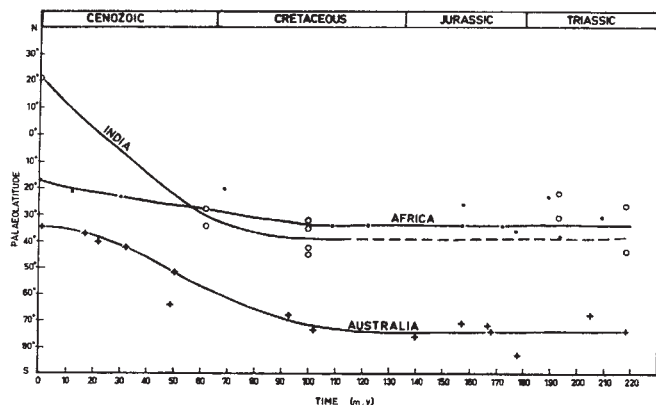


Fig. 6 Palaeomagnetic palaeolatitudes of some Gondwanan continents for Mesozoic and Cenozoic time. Palaeolatitudes of Australia (Canberra) designated by crosses, Africa (Salisbury) by dots, India (Nagpur) by circles; see refs. 29–31.

extent of the west coast of peninsular India appear from recent radiometric age determinations to have erupted partly or entirely in earliest Tertiary times (59 to 64 million years; ref. 24); stratigraphic data favour a Late Eocene age for the inception of Australia's southern continental margin (ref. 25 and J. J. V., to be published).

The south-west sector of the Indian Ocean is bisected by a narrow, fractured, symmetrical ridge of north-east trend, which is seismically active but apparently devoid of a bilaterally symmetrical pattern of magnetic anomalies²². These may be the marks of a ridge which has ceased to spread but which now acts principally as a fracture zone^{26,27}. The north-east sector is similarly bisected by a lineament of northerly trend, and like the south-west sector has so far yielded no decipherable pattern of magnetic anomalies. The lineament, the Ninetyeast Ridge, is an asymmetric, horst-like structure in oceanic crust^{19,22}. The apparent lack of a decipherable pattern of magnetic anomalies in the south-west and north-east sectors of the Indian Ocean suggests that these areas of seafloor may be pre-Cenozoic; this is confirmed by core samples of Cretaceous sediment from oceanic sites off South Africa and Madagascar and of reworked Cretaceous sediment from the centre of the basin which extends from Australia to the Ninetyeast Ridge²². The geology of the adjoining continental margins also favours a Cretaceous age for their inception. Deep sea sediments were deposited in several places along the rifted western continental margin of Australia in the Late Cretaceous, while along the opposing eastern margin of India the same time interval was marked by a phase of marine transgression which deposited sediment locally

on Pre-Cambrian basement¹⁷. Along the east coast of South Africa and Mozambique "no marine Jurassic formations are known. . . . The earliest marine deposits there are Neocomian" (Early Cretaceous²⁸).

Palaeomagnetic indications of continental motions (Fig. 6) are consistent with the Cretaceous–Cenozoic timing of Gondwanaland dispersal indicated by the geology of the Indian Ocean. It can be inferred^{29–31} that Africa, Australia—and perhaps India too—remained latitudinally static during most of the Mesozoic. All three began to drift north in the mid-Cretaceous—fifteen, forty and sixty degrees of latitude approximately for Africa, Australia and India—in a movement which persists to the present. The discrepancies in the magnitudes of the northerly components of movement suggest that large mutual displacements were associated with this late Cretaceous–Cenozoic drift.

It seems preferable to restrict an analysis of Gondwanaland dispersal to the motions of continents relative to one another and to the intervening ridge systems, rather than in relation to the geographic poles, until adequate palaeomagnetic data are available for east Antarctica. Our model for the dispersal of Gondwanaland (Fig. 7) therefore uses the central segment of the Indian Ocean Ridge system as an arbitrary datum to which the motions of the continents and oceanic plates have been related. (For a discussion of the continental motions which can be deduced from seafloor spreading and palaeomagnetic data, see Franchetau and Sclater³².) Africa/India separated from Australia/Antarctica during the Cretaceous, along an axis which includes the south-west branch of the Indian Ocean Ridge system and the Ninetyeast Ridge (Fig. 7a, b). At the beginning of the Cenozoic, dilation commenced along the currently spreading section of the Indian Ocean Ridge system (Fig. 7c), first in the north-west and then in the south-east. India moved from its Gondwanaland location adjoining East Africa to its present position and Australia separated from Antarctica (Fig. 7d) in the Cenozoic.

Our concept of the configuration and dispersal of Gondwanaland does not involve any large rotation of the continents such as the 45° rotation of India implicit in those reconstructions which place the west coast of India parallel to the east coast of Africa (for example, Fig. 4, inset). It is in this respect consistent with the characteristics of the Indian Ocean which yield no evidence of any such rotation; the floor of the north-west Indian Ocean, which might provide evidence of India's motion, is cut by numerous fractures of north-east–south-west trend³³, and the spreading axis which these fractures transect (Carlsberg Ridge) lies parallel to the western continental margin of peninsular India.

Our hypothesis also provides an integral place for the

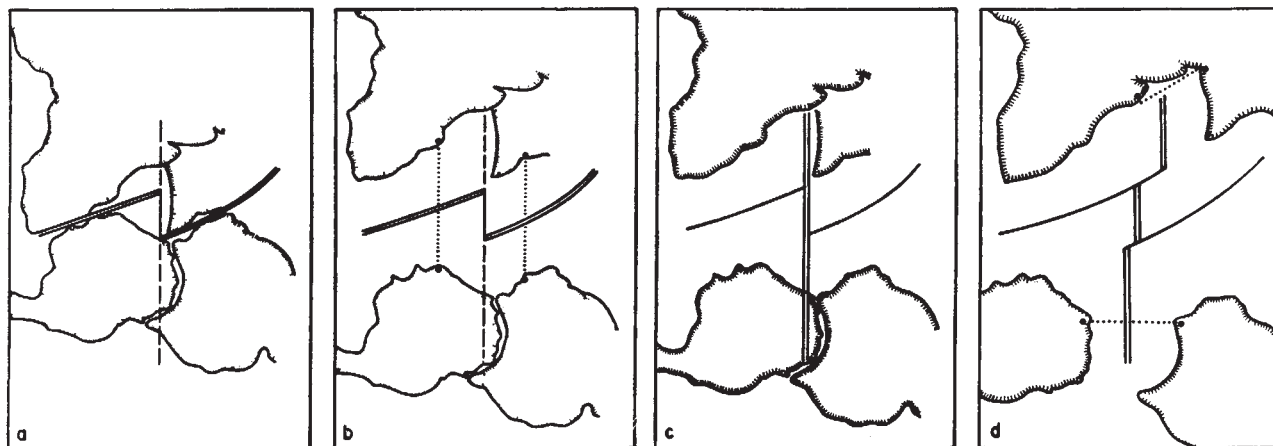


Fig. 7 Dispersal of Gondwanaland. a and b, Beginning and end of Cretaceous phase of dispersal. c and d, Beginning and present state of Cenozoic phase of dispersal. Heavy lines, crustal plate boundaries which may be passive (broken lines), or acting as faults (single lines) or spreading ridges (double lines). Lines of small dots indicate paths of displacement between once contiguous points on continents indicated by large dots. Central segment of Indian Ocean Ridge system taken as datum. Fig. 5 is used as base.

microcontinents of the Indian Ocean. All concentrate naturally in a median position when the deduced motions of the macrocontinents around the Indian Ocean are reversed, and fill the triangular space in our reconstruction (Fig. 4). Entities such as the Chagos-Laccadive and Mascarene plateaux are then most simply viewed as partially and wholly detached continental fragments shed in the wake of India.

A possible clue to the origin of our "Gondwanaland triangle" is contained in Fig. 7a where its boundaries are shown to enclose a displacement of the proto-Indian Ocean Ridge. If this displacement developed by transform faulting before continental dispersal, as implicit in Fig. 7a, one can readily envisage the resulting stresses leading to close fracturing in the immediately overlying portion of the Gondwanaland continental plate, and disintegration during drift.

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Cosmological Evolution in Radiogalaxies

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The evidence for cosmological evolution in radiogalaxies is now stronger, and the shortness of the time scale for this evolution (10^9 years) compared with the typical ages of galaxies poses a serious problem for the conventional view of galactic history.

THIS article is a refinement of a rough argument presented some time ago¹ that the properties of radiogalaxies have changed significantly during the past 10^9 years or so. This result is more important than the fact that quasars also show this kind of evolutionary effect^{2,3}, because we know a good deal about galaxies. The age of our own galaxy, for example, is believed to be more than 10^{10} years and, apart from nuclear activity^{4,5}, shows little sign of dramatic change in recent times. Other nearby galaxies have stellar populations similar to our own, though in different proportions⁶.

Some possible interpretations of rapid and recent evolution in radiogalaxies are: (i) All galaxies are changing significantly over a time scale of 10^9 years. If this interpretation is valid, why have no evolutionary effects been seen in the optical galaxies? (ii) Radiogalaxies are not typical galaxies, but have ages nearer 10^9 years. Burbidge⁷ has emphasized that there is lack of evidence for a stellar component in some radiogalaxies; also strong optical variations have been seen in some N galaxies^{8,9}, and the nearest radiogalaxy, M87, has been found to have vast outer extensions^{10,11}. But apart from these anomalies, there is no reason to suppose that radiogalaxies differ from normal, old, elliptical galaxies except in their above average optical luminosity. Sandage¹² finds a linear Hubble plot for these objects to a redshift of 0.46, and there is no evidence for a dependence of colour on redshift¹³ (surely a remarkable coincidence if strong evolutionary effects are present). (iii) The radio components are the products of interactions of outbursts in the parent galaxies with a universal medium which changes with epoch^{14,15}. This medium could, for example, be ionized gas, and may have the useful effect of confining the relativistic plasma which is often postulated to have been ejected from the nucleus of the

parent galaxy. The fact that the dynamics of matter within 10^6 light years of a massive elliptical galaxy will be controlled by the gravitational attraction of the galaxy rather than by the expansion of the universe seems, however, to have been overlooked. (A fourth possibility which must always be borne in mind is that the evolutionary effect is an apparent one caused by the wrong choice of cosmological model; this would show up whichever class of objects were investigated.)

Evidence for Evolution

The detailed radio maps of 220 sources from the 3C catalogue¹⁷⁻¹⁹, obtained with the Cambridge 1-mile telescope, have led to a homogeneous set of 98 reliable identifications of 3C sources with galaxies. Use is only made of those identifications in which there is one optical object associated either with a peak in the radio brightness distribution or with the axis joining the two components of a double source.

An estimate of the number of these that are chance superpositions can be made as follows: Let I be the number of identifications (quasars or galaxies), A be the number of ambiguous cases, E be the number of empty fields, C be the number of chance identifications (really empty fields), then assuming the ambiguous cases are due to chance superpositions on genuine identifications

$$\frac{C}{E+C} = \frac{A}{I-C}$$

In the present case, $I = 139$, $A = 22$, $E = 50$ (two are galactic sources, seven are obscured fields) so $C = 6$ or 111. The number of chance identifications with galaxies is only about 4 if the latter solution is ignored. An important point to note is that the combination of good radio positions with detailed maps of radio source structure leads to a considerable reduction in the number of chance identifications.

Two of these 98 identifications are with nearby spirals which are weak emitters (3C231 and 272.1). Thirty-nine of the remaining 96 have known redshifts and these define a mean relation between visual magnitude V and redshift z :

$$V = A + 5 \log_{10} z + Bz \quad (1)$$

with $A = 20.5$, $B = 5$ and an r.m.s. dispersion of 0.73 magnitudes. Most of this uncertainty is due to the approximate magnitude estimates; one source in 20 will lie more than 1.5 magnitudes from the mean relation. Equation (1) may be used to estimate the redshift of the remaining galaxies from their estimated visual magnitude with an uncertainty which will be correctly allowed for below by a weighting procedure.

If these estimates are treated as the actual redshifts, the luminosity-volume test^{2,3} may be applied by examining the distribution of radio luminosity at 178 MHz, $\mathcal{J}_{178} = \log_{10} P_{178}$ (where P_{178} is in units of W sterad⁻¹ Hz⁻¹) against

$$x = \mathcal{V}(z)/\mathcal{V}(z_{\max}) \quad (2)$$

where $\mathcal{V}(z)$ is the comoving volume of the sphere of matter with redshift less than or equal to z , and $z_{\max}$ is the redshift at which the source would disappear out of the observer's sample (defined by the 3C limit and by the plate limit, taken as $V_{11m} = 20$). This distribution is shown for the Einstein-de Sitter cosmological model in Fig. 1; it is not very much different in other relativistic cosmological models with $q_0 \geq -1$.

If these objects were distributed in space with uniform coordinate number density, then in any range of luminosity the quantity x would be uniformly distributed in (0, 1), with mean 0.5 and standard deviation $\sqrt{1/12}$ (see ref. 16). The distribution is strikingly nonuniform for $\mathcal{J}_{178} \geq 25.5$, and for all 95 radio galaxies brighter than magnitude 20, the mean value of x , $\bar{x} = 0.631$, is significantly different from 0.5 at the 99.9% level (using Student's $t = \sqrt{12n}(\bar{x} - \frac{1}{2})$ —see ref. 16). For $\mathcal{J}_{178} < 25.5$, $\bar{x} = 0.492$, and for $\mathcal{J}_{178} \geq 25.5$, $\bar{x} = 0.716$, showing that the departure from uniformity is entirely due to the stronger radiogalaxies.

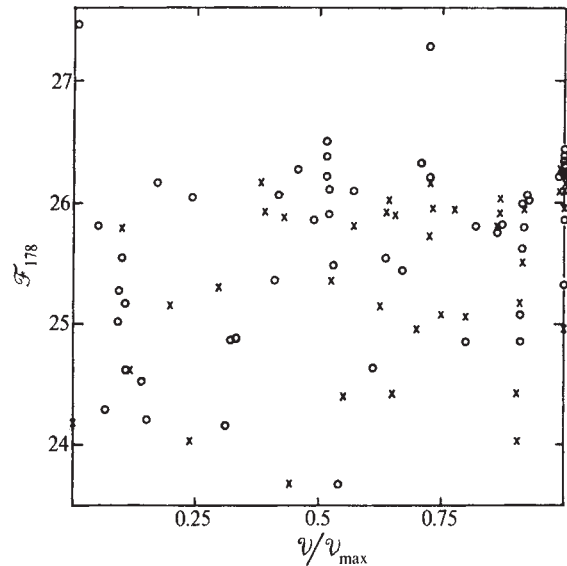


Fig. 1 Radio luminosity against $\mathcal{V}/\mathcal{V}_{\max}$ for 95 3C radio-galaxies. Circles: sources with projected linear dimensions greater than 100 kpc; crosses: sources with projected linear dimensions less than 100 kpc, including all resolved single sources and unresolved sources.

The effect of confining attention to galaxies brighter than 19.5, 19, 18.5 and 18 magnitudes respectively is shown in Table 1; the departure from uniformity is still significant for the stronger radiogalaxies. Chance identifications cannot explain this effect unless the number is very much greater than estimated above.

Fig. 2 shows the luminosity distributions for four equivalent volumes of observable space

$$(0 < x \leq 0.25, 0.25 < x \leq 0.5, 0.5 < x \leq 0.75, 0.75 < x \leq 1.0)$$

This distribution changes continuously from being almost square between $\mathcal{J}_{178} = 24$ and 26.5 for the nearest range, to one sharply rising towards higher luminosities for the farthest.

Correlations

There is no clear correlation of spectral index α with x for a particular range of radio luminosity, although it is of course known that there is a correlation of α with luminosity^{20,21}. One odd effect is that among the stronger sources the dispersion in α —but not the mean—is larger for the more distant sources (0.14 for $x \leq 0.75$, 0.19 for $x > 0.75$).

Table 1 Dependence of x on Limiting Magnitude

V_{lim}	20	19.5	19	18.5	18
$\bar{x}$	0.631	0.603	0.604	0.556	0.542
n	95	81	72	57	50
t	4.4	3.2	3.1	1.5	
probability (%)	≤ 0.1	0.2	0.3	15	
$\bar{x}^*$	0.584	0.568	0.548	0.513	0.502
n^*	85.2	74.1	64.3	52.6	47.0
t^*	2.7	2.0	1.3		
probability (%)	0.9	5	20		
Strong radiogalaxies only ($\mathcal{J} \geq 25.5$)					
$\bar{x}$	0.716	0.692	0.715	0.665	0.671
n	59	45	36	21	14
t	5.7	4.5	4.5	2.6	2.2
probability (%)	≤ 0.1	≤ 0.1	≤ 0.1	2	4
$\bar{x}^*$	0.652	0.641	0.619	0.566	0.537
n^*	49.2	38.1	28.3	16.7	11.3
t^*	3.7	3.0	2.2	0.9	
probability (%)	0.1	0.5	3.5	> 25	

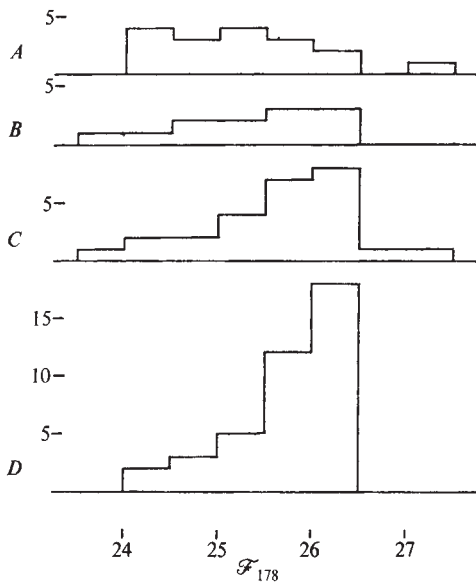


Fig. 2 Luminosity distributions for four equivalent volumes of observable space: A, $0 < x \leq 0.25$; B, $0.25 < x \leq 0.5$; C, $0.5 < x \leq 0.75$; D, $0.75 < x \leq 1$.

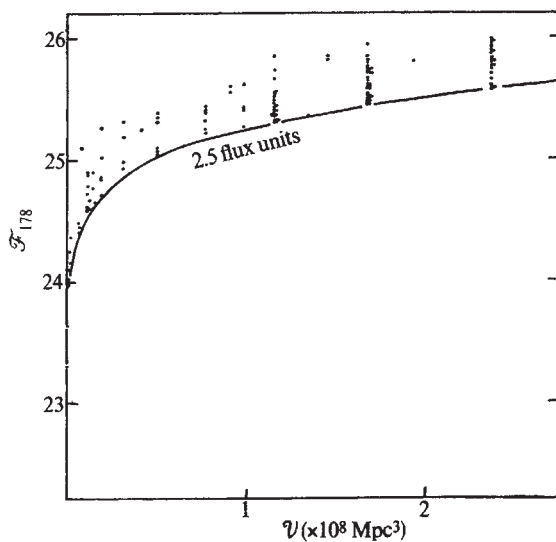


Fig. 3 Radio luminosity volume diagram for 130 4C radio-galaxies with $S_{178} \geq 2.5$ f.u.

The resolved sources show no significant difference between the values of $\bar{x}$ for different types of source (double, elongated, single or complex). The unresolved sources, however, give much larger values of $\bar{x}$, both for weak and strong radio-galaxies, than the resolved sources; the most significant part of the difference of $\bar{x}$ from $\frac{1}{2}$ is due to these unresolved sources. This is consistent with their being more distant objects of the same type as the resolved sources, but confirmation must await higher resolution studies.

If my interpretation (iii) of this evolutionary effect is correct, some correlation with linear size would be expected, in the sense that sources of small linear extent are less likely to show the effect. A projected linear size can be calculated for each object using the angular separation of double sources and the largest angular size of the others. If the objects are divided into those larger and smaller than 100 kpc, it is found that $\bar{x}$ is significantly greater for the smaller group (which includes all the single and unresolved sources). The radio sources in the latter group are not very much greater in size than the parent

galaxies because giant elliptical galaxies can extend to radii of 50–80 kpc (ref. 6). Thus the evolution of these objects must be governed by some effect connected with the rate or violence of the events giving rise to the sources, or with the spatial frequency of the parent galaxies. The less severe evolution apparent for the more extended sources indicates that the effect of any universal matter or radiation field must be to reduce the apparent rate of evolution.

Redshift Uncertainties

We must now estimate the effect of the r.m.s. uncertainty of 0.73 magnitudes in calculating z from the visual magnitude V using equation (1). Each identification for which the redshift is not known is treated as a continuous gaussian distribution with mean V and standard deviation $\sigma = 0.73$ and not as a discrete object with magnitude V .

$$\text{Thus } x^*(V) = \int_{-\infty}^{V_{\text{lim}}} x(Y) \frac{\exp - (Y-V)^2/2\sigma^2}{\sqrt{2\pi}\sigma} dY$$

where $x(Y)$ is calculated from equation (2) using equation (1). We must also treat each identification not as 1 unit, but as

$$\delta n^* = \int_{-\infty}^{V_{\text{lim}}} \frac{\exp - (Y-V)^2/2\sigma^2}{\sqrt{2\pi}\sigma} dY \text{ units}$$

so that $\bar{x}^* = \Sigma x^*/n^*$, where $n^* = \Sigma \delta n^*$. Individual values of $(x^*/\delta n^*)$ do not differ greatly from x ; the reason for this is that $\left(\frac{\partial x}{\partial V}\right)_s$ is very small²². The fact that sources near the plate limit, which have larger values of x , contribute to $\bar{x}^*$ with reduced weight (for example, $\delta n^* = \frac{1}{2}$ if $V = V_{\text{lim}}$) means that $\bar{x}^*$ is smaller than $\bar{x}$. Corresponding values are tabulated in Table 1; the distribution is still significantly nonuniform after this correction has been applied, especially for sources with $\mathcal{J}_{178} \geq 25.5$.

Rate of Evolution

Following reference 1 we correct the luminosities of sources or weight the volume according to different types of evolution until $\bar{x}^*$ is reduced to 0.5; the values of the parameters required are indicated in Table 2. The characteristic time scale for luminosity evolution is 1.3×10^9 years, and for density evolution $0.7 + 10^9$ years.

Merkelijn (preprint; 1970) has examined the distribution of radiogalaxies identified with Parkes sources and confirms the evolutionary effect reported previously¹. The conclusion is not entirely independent, however, since 40% of this Parkes sample are in fact also 3C sources, and the redshift data are almost identical (only one additional redshift). It is clearly important to have the redshifts of a sample of southern hemisphere radiogalaxies comparable with the 3C sample.

To investigate the distribution with respect to volume of the weaker radiogalaxies ($23.5 \leq \mathcal{J}_{178} < 25.5$) it is necessary to have a sample complete to an appreciably fainter flux level than the 3C limit (9 flux units; 1 f.u. = 10^{-26} W m⁻² Hz⁻¹). Olsen²³ has provided identifications with galaxies for 130 4C sources²⁴

Table 2 Choice of Parameters to reduce x^* to 0.5

Type of evolution	Density	Luminosity
Negative power law dependence on scale factor, $(1+z)^q$	$Q = 10 \pm 4$	6 ± 2
Negative exponential dependence on scale factor, $\exp Q(1 - 1/(1+z))$	$Q = 12 \pm 5$	7 ± 3
Negative exponential dependence on cosmical time, $\exp \frac{2Q}{3}(1 - (1+z)^{-3/2})$	$Q = 14 \pm 6$	8 ± 3
Corresponding time scale if Hubble time is 10^{10} years	0.7×10^9 years	1.25×10^9 years

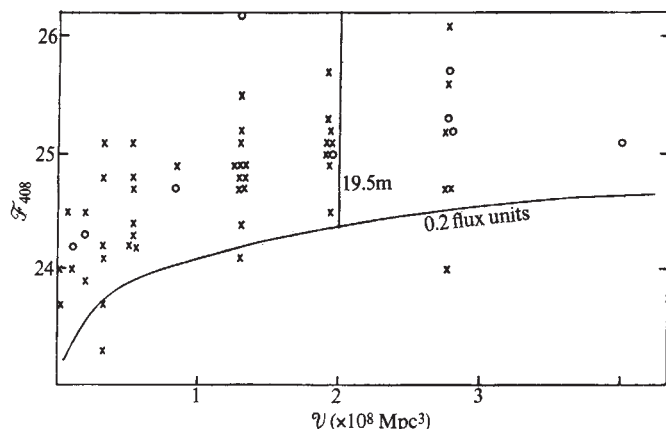


Fig. 4 Radio luminosity volume diagram for 70 radiogalaxies identified with sources in the Windram and Kenderdine survey²⁵ $S_{408} \geq 0.2$ f.u. Circles denote uncertain identifications.

with $S_{178} \geq 2.5$ f.u., and has given estimated photored magnitudes for these. Estimates of the redshifts can be obtained by using equation (1) above, together with Oke and Sandage's expression¹³ for $(V-R)_{\text{corr}}$ as a function of redshift for the standard giant elliptical galaxy. Approximately

$$(V-R)_{\text{corr}} = 0.8 + 1.25 z$$

to the accuracy needed here and so the parameters required in equation (1) are $A = 19.7$, $B = 3.75$. Fig. 3 is the radio luminosity volume diagram for these 4C radiogalaxies, and shows very striking nonuniformity ($\bar{x} = 0.74$), particularly for $\mathcal{J}_{178} \geq 25.0$. The survey by Windram and Kenderdine²⁵ provides a sample of radiogalaxies with $S_{408} \geq 0.2$ f.u., and Fig. 4 shows the radio luminosity volume for these sources. Windram and Kenderdine believe their identifications to be complete to magnitude 19.5 and the corresponding limit is indicated. For $\mathcal{J}_{408} \geq 24.7$ (corresponding to $\mathcal{J}_{178} > 25.0$) there

are again significantly more sources in the further half of the observable volume than in the nearer, suggesting that the evolution found previously¹ and confirmed here operates at least down to this luminosity.

This rapid, recent evolution in the radiogalaxy population clearly conflicts either with long established views about galactic history or with the most widely supported cosmological models.

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Amino-acid Sequences of Kangaroo Myoglobin and Haemoglobin and the Date of Marsupial-Eutherian Divergence

by

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Differences in the amino-acid sequences of corresponding globin proteins have been used to calculate when marsupials and eutherians diverged in evolution.

THE first suggestions that amino-acid sequences of homologous proteins might be the basis of quantitative phylogenetic schemes

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stemmed from the observations¹ that the haemoglobins of man and gorilla are very similar, but that horse haemoglobin, clearly homologous, differs at many sites. Several methods^{2,3} of varying complexity have since been used to relate amino-acid sequences to phylogeny and phylogenetic trees have been based on proteins such as cytochrome *c*, haemoglobin and fibrinopeptides. Providing a time scale for these schemes of evolution has not as yet been particularly successful, however. One difficulty is to demonstrate that the rate of evolution of the protein concerned has been in some cases constant, and since this can only be done in a statistical sense, many amino-acid

per 100 residues, Y , such that

$$Y = \frac{t}{D} = \frac{2nt}{100d} \quad (2)$$

Because so few complete sequences are available, we first included the kangaroo data to calculate an average rate of amino-acid substitution for each globin chain. The matrices of Tables 2, 3 and 4 show the values for d . The dates of divergence of species used were taken from Fig. 1, which is based on information given by Romer¹⁴. We calculated Y for all sequence comparisons of each polypeptide, that is, a total of 10 comparisons for myoglobin, 28 for haemoglobin α -chain, and 15 for haemoglobin β -chain. The results obtained are shown as frequency histograms in Fig. 2. More amino-acid sequences would be desirable, particularly in the case of myoglobin, but the α - and β -chain results approximate a normal distribution.

Table 5a shows the mean values for Y . The evolutionary rate of each globin seems to be statistically constant, although the standard deviations are large due to the small sample size.

Divergence of Marsupials from Eutherians

To obtain a date for marsupial-eutherian divergence, we repeated the calculations but omitted all comparisons involving kangaroo sequences. This avoids using the data in a circular fashion. Table 5b shows the resulting values for Y . These values were then used to calculate the mean time of divergence of marsupials from eutherian mammals for each polypeptide by using equation (2). Table 3 gives the results. Three independent estimates using the three different protein chains give very promising results. The three estimates agree both with each other and with the palaeontological evidence¹⁵, which suggests that divergence probably occurred as early as the beginning of the Cretaceous period, 130 million years ago (see also ref. 16).

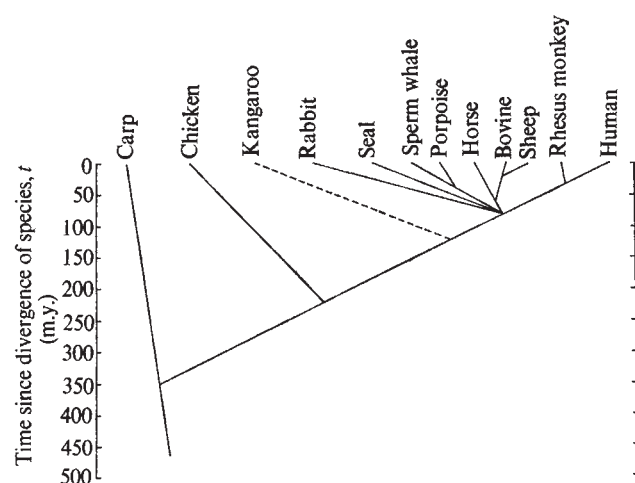


Fig. 1 Phylogenetic tree from which the dates of divergence of species used in the calculations were taken. This scheme is based on palaeontological information given by Romer¹⁴.

Radiation of the Macropodidae

We have applied our method to β -haemoglobin chains of other macropodids. Because amino-acid sequences are incomplete, estimations of amino-acid differences (based on amino-acid compositions of tryptic peptides) must be considered as minimal. The β -chain of the red kangaroo differs from that of the grey kangaroo by a single substitution, that of glycine for alanine at residue β 56. Many other species of wallaroo and wallaby also have glycine at this site, and although these β -chains have not been studied in detail, only one or two changes

in amino-acid compositions of tryptic peptides have been detected, indicating a recent radiation of macropodine species.

By contrast, the potoroo *Potorous tridactylus* (Kerr, 1792) has at least sixteen changes in the β -chain sequence compared with the grey kangaroo. Applying the same calculations as before, this gives a most recent date for divergence of the potoroine-macropodine lines as about 57 m.y. ago. Material referred to the living potoroine genus *Bettongia* has been found in the Ngapakaldi fauna of South Australia tentatively dated as Oligocene (beginning 34 m.y. ago). Later beds yield remains of a possibly distinct, and as yet unnamed, macropodid group (? subfamily) in some respects intermediate between Potoroinae and Macropodinae. The earliest remains referable to the Macropodinae occur in the Kutjamarpu fauna of Miocene age¹⁷. If the Ngapakaldi potoroine is a *Bettongia* this suggests that the Potoroinae may have diverged at least 57 million years ago. But because the rate of substitution is only statistically constant, present estimates derived from amino-acid sequences must be regarded as tentative.

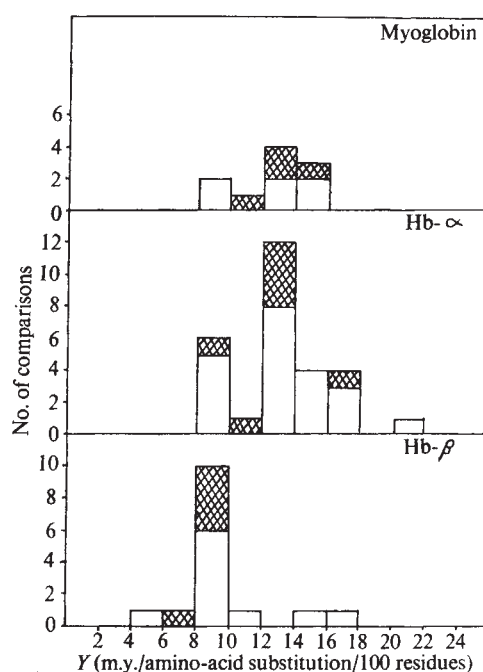


Fig. 2 Frequency histograms for the calculated values of Y , the years per amino-acid change per 100 residues, for myoglobin and haemoglobin α and β chains. The areas cross-hatched indicate comparisons involving kangaroo sequences.

Constant Rate of Protein Evolution

Our calculations support earlier predictions^{1,7}, that each globin chain has undergone evolutionary change at a constant rate. This implies that further marsupial amino-acid sequence work may enable dates of divergence of other members of the Marsupialia to be calculated. The fossil record of marsupial

Table 2 Number of Amino-acid Sequence Differences between Myoglobins

	Horse	Seal	Porpoise	Whale	Kangaroo
Horse	0	20	16	19	25
Seal	20	0	17	26	27
Porpoise	16	17	0	15	28
Whale	19	26	15	0	31
Kangaroo	25	27	28	31	0

Table 3 Number of Amino-acid Sequence Differences between Alpha Globins

	Human	Monkey	Horse	Bovine	Rabbit	Kangaroo	Chicken	Carp
Human	0	4	18	17	25	24	35	71
Monkey	4	0	16	16	25	23	35	71
Horse	18	16	0	18	25	26	40	70
Bovine	17	16	18	0	25	26	38	68
Rabbit	25	25	25	25	0	34	44	74
Kangaroo *	24	23	26	23	34	0	37	69
Chicken	35	35	40	38	44	37	0	75
Carp *	71	71	70	68	74	69	75	0

* Sequences are of 141 residues except for carp (143 residues) and for the 129 out of 141 residues at present allocated for kangaroo α -chain.

Table 4 Number of Amino-acid Sequence Differences between Beta Globins

	Human	Monkey	Horse	Sheep	Rabbit	Kangaroo
Human	0	8	26	26	14	38
Monkey	8	0	28	27	16	36
Horse	26	28	0	33	25	46
Sheep B	26	27	33	0	29	43
Rabbit	14	16	25	29	0	37
Kangaroo	38	36	46	43	37	0

Table 5 Average Rate of Evolution of Globin Chains

	Myoglobin	Haemoglobin α -chain	Haemoglobin β -chain
(a) Mean $\pm$ s.d. (N) *	12.5 ± 2.3 (10)	13.4 ± 3.0 (28)	9.6 ± 2.8 (15)
All sequences			
(b) Mean $\pm$ s.d. (N)	12.1 ± 2.8 (6)	13.6 ± 3.3 (21)	10.0 ± 3.3 (10)
Omitting kangaroo sequences			

Figures give million years per amino-acid change per 100 amino-acid residues.

* N is the number of comparisons involved.

Table 6 Calculated No. of Years Elapsed since Marsupial-Eutherian Divergence

Myoglobin	Hb- α	Hb- β
111×10^6	139×10^6	137×10^6
$(85-136) \times 10^6$	$(123-154) \times 10^6$	$(104-170) \times 10^6$

Ranges shown are the 95% confidence limits calculated from standard errors as in Table 5.

evolution is sparse, and estimation of such dates could be used to determine the relationships between the various Australian taxa and between Australian and American marsupials; but many more complete amino-acid sequences are required to increase the precision of the method. We have frequently found that the amino-acid sequence of a tryptic or chymotryptic peptide from kangaroo proteins^{9,10} differs from that predicted¹⁸. We have not therefore included any of the many sequences published which are based on homology unless they are very near to completion as defined by Dayhoff³. Examination of tryptic peptide maps is of very limited use in phylogenetic studies. The potoroos β -chain peptide map shows only

one peptide difference from that of the grey kangaroo⁹, whereas there are at least sixteen changes in amino-acid sequence. Seal¹⁹ has recently reported that all species sampled of the Phocidae, Otariidae, Canidae, Ursidae, Procyonidae and Mustelidae have a major haemoglobin identical in electrophoretic mobility, tryptic peptide map, and amino-acid composition, and concludes that haemoglobin evolution has ceased in all these families. We suggest that a closer examination might reveal many alterations in amino-acid sequence not detectable by these methods.

We do not understand why the rate of evolution of a given protein is constant. If the major contribution to evolutionary change is by "selectively neutral" substitutions^{7,20}, populations should be exceedingly heterogeneous. It has been estimated²¹ that 1 in 200 of the European human population has an abnormal haemoglobin. This calculation is based on charge differences found between haemoglobins. But substitutions which do not involve charge differences should have less effect on the molecule, and therefore would suffer less loss through the rapid selecting out of harmful mutations. The frequency of occurrence of human haemoglobin variants may be much higher than this estimate, but there does not seem to be widespread heterogeneity in haemoglobin amino-acid sequences.

But it is difficult to see why the rate of natural selection should be constant for periods in excess of 10^8 yr in several different lineages and why natural selection should operate on all amino-acid substitutions.

Assuming that the rates of random drift or of natural selection are constant does not take account of any effects due to varying generation times and population sizes. Although the reasons are obscure, protein evolution seems to have proceeded at a constant rate, at least in the haemoglobins and myoglobins. But we should emphasize that complete amino-acid sequences are required for these calculations and that it is essential to eliminate uncertain residues (such as Asx, Glx)³.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Planet, Pulsar, "Glitch" and Wisp

ONE or more planets may be orbiting the pulsar in the Crab Nebula. Richards *et al.*¹ inferred the presence of a planet from the sinusoidal behaviour of the residuals in the pulse arrival time data of NP 0532 after the first and second derivatives of the pulsar period had been removed. The sinusoidal character of the residuals has, however, been queried^{2,3}. Michel⁴ has attributed the period discontinuity observed last autumn^{5,6} (the so-called "glitch") to a planet in a highly eccentric orbit sweeping close to the pulsar. And the Princeton group⁷ have tentatively fitted their pulse arrival time residuals by invoking three planets!

We wish to discuss other observational consequences of the existence of a planetary system around NP 0532. In particular, we suggest that material evaporated from a planet in an eccentric orbit could be responsible for the brightening of the "thin, wisp" in the Crab Nebula which occurred after the "glitch"⁸ and for the increases of dispersion measure observed during the past year for NP 0532 (ref. 9).

Such a suggestion is tenable only if a planet initially in orbit around the Crab Nebula's parent star could have survived until the present time. Three things might endanger it: the drag of the extended atmosphere surrounding the parent star during a red giant phase; the supernova event; and the high luminosity, now or in the past, of the pulsar itself. We shall consider these in turn.

The luminosity of a 3 $M_{\odot}$ star during its hydrogen shell burning phase is $\sim 10^3 L_{\odot}$ (ref. 10), and at a distance $r \approx 5 \times 10^{12}$ cm the effective temperature would be $\sim 2,500$ K. (The reasons for this choice of numbers will become apparent later.) Although a planet would rapidly lose its atmosphere at this temperature, only a small fraction of the energy would actually go into evaporation, and we estimate that a planet of a few Earth masses would survive heating during this phase of stellar evolution. A more serious effect, however, may be the frictional drag that arises if the stellar atmosphere extends beyond the orbit of the planet. If the planet sweeps up an amount of material comparable to its own mass it will spiral into the star. This will happen if the density of the stellar envelope at the radius of the planet's orbit exceeds $\sim 10^{-5} t^{-1} \text{ g cm}^{-3}$, when t is the duration of the phase in years. Iben's model¹⁰ does not, however, have a radius as large as 5×10^{12} . The planet will probably also survive the effects of heating during the even more luminous, but much briefer, stages of evolution following helium ignition. The effects of atmospheric drag in these phases are hard to estimate because the properties of the outermost layers of the star are sensitive to various uncertainties.

When the supernova explosion ejects a fraction f of the mass of the star, the sudden reduction of the gravitational force charges an initially circular planetary orbit into one with eccentricity $e = f/(1 - f)$. Thus, a planet which had survived the pre-supernova phases would not remain gravitationally bound if the star lost more than half its mass (leaving aside the unlikely

possibility that the orbit was initially highly eccentric, and the explosion occurred when the planet was close to apastron). Models of the Crab Nebula in which the filaments contain $\gtrsim 2 M_{\odot}$ (refs. 11 and 12) would therefore exclude planets. Even when $f < \frac{1}{2}$ (as seems probable for the Crab¹³) the planet may be expelled or destroyed by the violent impact of ejecta from the explosion. This problem has been discussed by Colgate¹⁴, who estimates that a planet of mass M , and density comparable with that of the Earth, could survive provided that its periastron distance were $\gtrsim 2.5 \times 10^{12} (M/M_{\oplus})^{-2/9}$ cm. The present orbit of any such planet would probably be highly eccentric, as a consequence of the supernova explosion and the associated mass loss from the exploding star.

Finally we must consider the rate at which energy from the pulsar is likely to boil away material from a planet. This affects the survival of a planet to the present day, and also relates to possible observable manifestations of its presence. To be more specific, we shall consider a planet of a few Earth masses with periastron distance 5×10^{12} cm (0.35 a.u.) and orbital eccentricity e . If the mass of the pulsar is $\sim 1.5 M_{\odot}$, the period would be $\sim 2[(1+e)/(1-e)]^{3/2}$ months.

The current total luminosity of NP 0531, as estimated from its slowing down rate and from the energetics of the Nebula, is $\sim 10^{38} \text{ erg s}^{-1}$. Some of this output, of course, emerges as pulsed emission, mainly at X-ray energies, but the bulk would be in the form of fast particles, or perhaps electromagnetic waves. As the blackbody temperature in the vicinity of the planet, near periastron, would be $\sim 6,000$ K the main effect of the pulsar on the planet may be to cause continual vaporization and evaporation from its surface. The amount of power intercepted by the planet when it is at a distance r from the pulsar is

$$\sim 7 \times 10^{28} \left(\frac{L}{10^{38} \text{ erg s}^{-1}} \right) \left(\frac{r}{10^{13} \text{ cm}} \right)^{-2} \left(\frac{M}{M_{\oplus}} \right)^{2/3} \text{ erg s}^{-1} \quad (1)$$

L is the luminosity of the pulsar, and we have assumed that the planet has the same density as the Earth. The escape energy from the planet's gravitational field is $\sim 6 \times 10^{11} (M/M_{\oplus})^{2/3} \text{ erg g}^{-1}$ (and the evaporation energy is probably $\lesssim 10^{12} \text{ erg g}^{-1}$). We can therefore set an approximate upper limit to the evaporation rate by supposing that all the energy impinging on the planet is used to eject material with the escape velocity. This limit is

$$\sim 10^{17} \left(\frac{r}{10^{13} \text{ cm}} \right)^{-2} \left(\frac{L}{10^{38} \text{ erg s}^{-1}} \right) \text{ g s}^{-1} \quad (2)$$

This could, for several reasons, be a serious overestimate of the actual mass loss rate. For example, much of the incident energy may be reflected or reradiated electromagnetically, and it is possible that the absorbed energy is used to eject a much smaller amount of material with a velocity correspondingly much greater than the escape velocity. The details of the mass loss plainly depend on the composition of the planet and on

the character of the incident radiation. We do not attempt a full discussion here. Instead we shall assume that the rate of mass loss (at least when $r \lesssim 10^{13}$ cm) is within an order of magnitude of the value given by equation (2). And obviously, if the planet can survive with the mass loss rate given by equation (2), it will do so, *a fortiori*, for any smaller rate.

We observe that, with the present luminosity of NP 0531, a planet of, say, $5 M_{\oplus}$ ($\sim 10^{28}$ g) could survive for several thousand years, even in an orbit with periastron distance $\sim 5 \times 10^{12}$ cm. The pulsar would, however, have been more luminous, and the evaporation rate greater, in the past. The measured deceleration rate of NP 0531 implies, on the basis of the simple "oblique rotator" model¹⁵, that the rotation rate was initially only twice as fast as it is now. A planet would still survive even when this faster rotation is taken into account. (If the neutron star were initially spinning with almost its break-up angular velocity, and all the rotational energy were radiated electro-magnetically, a planet would probably have been destroyed. The hypothesis of such rapid initial rotation leads to other problems¹⁶, however, unless the principal energy loss results from gravitational radiation.)

It thus seems at least possible that a planet of a few Earth masses might still be found in an orbit of major axis $\gtrsim 10^{13}$ cm around NP 0531, having survived the red giant, supernova, and early pulsar phases of its parent star.

The mass loss would occur predominantly near periastron. This follows from the r^{-2} dependence of 2, but we expect the effect to be accentuated because a smaller fraction of the incident energy will give rise to evaporation when the planet is cooler. We may therefore expect a planet with periastron distance $\sim 5 \times 10^{12}$ cm to lose $\sim 10^{23}$ g of material over the 1-2 week period when it sweeps closest to the pulsar.

What will be the fate of this material? If no further forces acted on it, the debris would form a trail behind the planet, and would expand transversely, with a speed $\gtrsim 10$ km s⁻¹ (the escape velocity from the planet). This diffuse tail would intercept a much larger fraction of the radiation from the pulsar than does the planet (for example, after one week it would cover $\sim 10\%$ of the solid angle around the pulsar) and so would be accelerated rapidly.

Taking a specific illustration, if 10^{23} g of matter, spread uniformly, intercepts 10% of the radiation from the pulsar, and all the intercepted radiation is absorbed or reflected (which is a reasonable assumption, because optical and X-ray photons, to which the material would be transparent, constitute only a small fraction of the pulsar's power output, and the material is surely opaque to 30 Hz radiation, as well as to relativistic particles) then the momentum of the radiation would impart a constant radial acceleration of $\sim 3,000$ ($L/10^{38}$ erg s⁻¹) cm s⁻², until the matter becomes relativistic. Hence it reaches relativistic speeds within a month, attaining a kinetic energy $\gtrsim 10^{44}$ erg.

Thus, each time the planet passes close to the pulsar, a cloud of material is ejected (in the plane of its orbit) at speed $\sim C$, in a manner reminiscent of a comet's tail. It is tempting to identify this "tail" with the "thin wisp". In this connexion it is interesting that the thin wisp lies in the equatorial plane of the pulsar, if the orientation of the rotation axis is inferred from the polarization properties of the Nebula¹⁷. If the changes in the thin wisp are indeed related to the "glitch", they must have propagated at $\sim C$. Scargle and Harlan⁸ estimate the energy involved as 10^{41} – 10^{45} erg, which is no problem on our proposed interpretation. If, on the other hand, the "glitch" was due to a starquake, the energy released would only have been $\sim 10^{40}$ erg and there is no obvious way in which the brightening of the thin wisp could have been triggered. The relationship of this evaporated material to the other wisps described by Scargle¹⁸ is not clear, but it is possible that the apparent ~ 2 year periodicities in the motion of the "main wisp" are in some way associated with the orbital period of a planet.

It is also interesting that the increases in the dispersion

measure of NP 0532 have been correlated with periods when the pulse arrival time has been particularly erratic, including the period just after the "glitch". The increase in dispersion measure from September 1969 to August 1970 has been 10^{16} – 10^{17} electrons cm⁻² (with an extra factor γ if the relevant electrons are relativistic)⁹. If the dispersion were due to material $\lesssim 10^{13}$ cm from the pulsar, only 10^{19} g would be involved. This is small compared with the estimated mass in the thin wisp. The extra dispersion could therefore be caused by a small fraction of the evaporated matter which is ejected (unlike the thin wisp itself) in our line of sight to NP 0532.

The material evaporated from a planet over the lifetime of the nebula may amount to about one Earth mass, which is negligible compared with the mass in the filaments. The material would, however, become relativistic, and would add substantially to the relativistic particle content of the Nebula.

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Variable Seafloor Spreading off Baja California

THE development of plate tectonics^{1,2} has led to the concept that the Earth's crust is divided into stable plates which were created at oceanic ridge crests, move as whole units and are subsequently destroyed in oceanic trenches. The question of where and how these three crustal elements intersect is one of the chief problems in the Earth sciences³.

The regions of Baja California and the Gulf of California are of great interest⁴⁻⁶, because it is in these areas that the East Pacific Rise and the North American crustal plate meet; a considerable amount of work has been done near the tip of Baja California in order to clarify the manner in which these two crustal features merge.

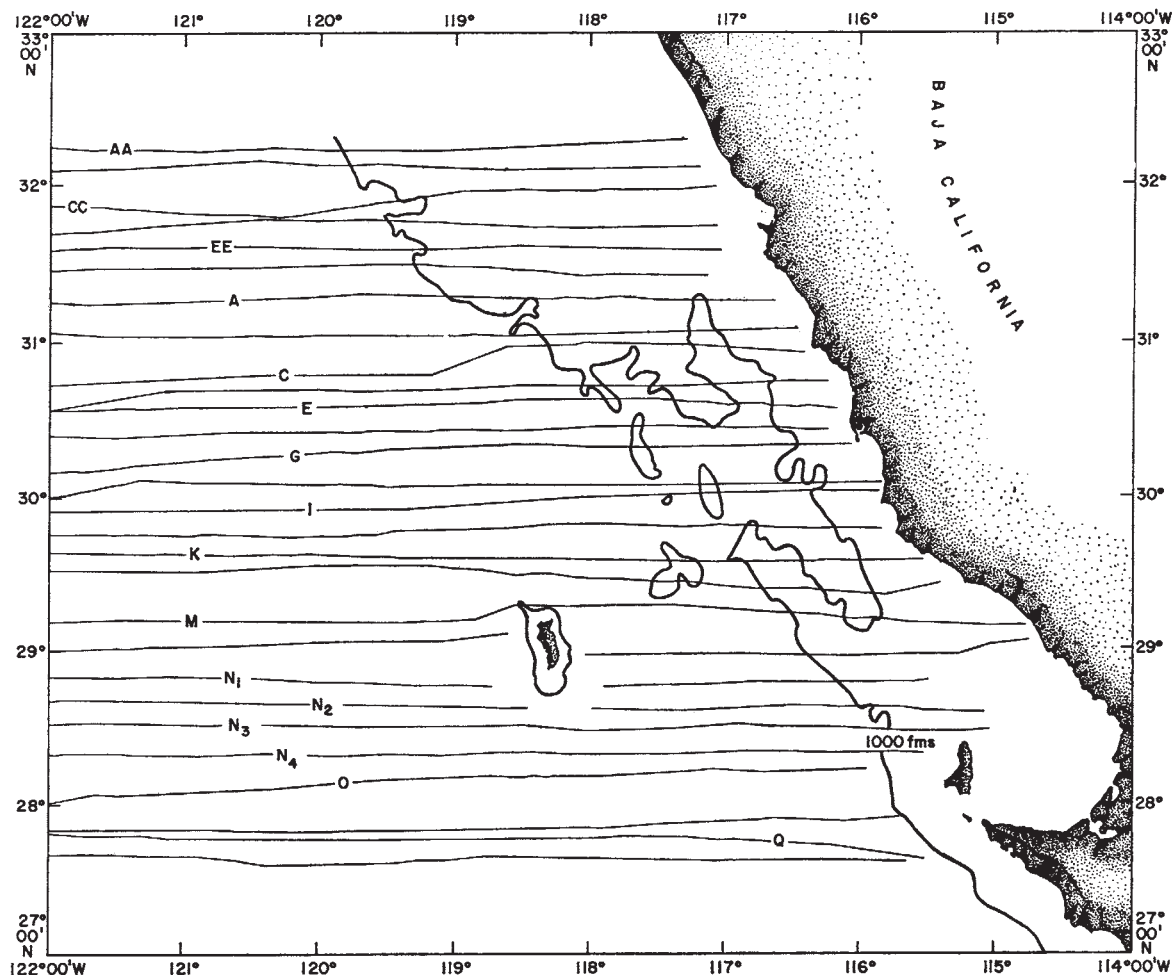


Fig. 1 Flight lines indicated as lettered lines (for clarity only every other line is labelled). Guadalupe is the island at approximately 29° N and 118° W. The 1,000 fathom contour is indicated by the sinuous solid line.

Chase *et al.*⁵ have investigated the area off the west coast of Baja California south of latitude 28° N. They show how the Miocene East Pacific Rise was deformed into a triple ridge junction by the approach of the North American plate from the north-east and emphasize that more data are required to the north of their area of study if it is to be known how one of the crustal plates formed by the creation of the triple junction is coupled to the continental plate. We have now acquired additional magnetic data in the region just north of the 28th parallel which will probably help to define the geological history of the area.

The area surveyed lies between 28° and 32° N and extends from the west coast of Baja California to longitude 122° W. Total intensity magnetic data were gathered in 12,000 km of east-west oriented flights during August and September 1969 and May 1970. Flight line spacing was approximately 15 km and the flight elevation was 180 m; positional information was obtained from Loran A, Doppler radar and visual sightings. The flight line locations are shown in Fig. 1.

The magnetic profiles were stacked as in Figs. 2 and 3 so that magnetic anomalies between adjacent flight lines could be easily correlated. The profile data represent residual magnetic anomalies which are obtained by removing the International Geomagnetic Reference Field from the total intensity magnetic data.

Krause⁷ has compiled all the geophysical and geological information from this area into a regional study, and more recently Atwater and Menard⁸ used Krause's data in their review of the magnetic lineations of the North-East Pacific. The data in this study are, however, more uniform and therefore the anomaly pattern can be seen in greater detail.

The seafloor spreading rates off Baja California were computed from the magnetic data of Figs. 2 and 3 and the time scales of Heirtzler *et al.*⁹ and Vine¹⁰ were used for assigning ages. The ages inferred, together with proposed correlations between adjacent profiles, are indicated in Figs. 2 and 3. The anomaly numbers of Heirtzler *et al.*⁹ were used with the subdivisions of Chase *et al.*⁵. Table 1 lists the computed spreading rates from each profile.

It is obvious from Table 1 that the spreading rate is non-uniform throughout the area covered by this study; Chase *et al.*⁵ also found variable spreading rates within the region south of 28° N latitude. This variable rate of seafloor spreading is, however, not random and Fig. 4 illustrates the spreading rate

Table 1 Computed Spreading Rates from Magnetic Profiles

Profile	Spreading rate (cm yr ⁻¹)	Profile	Spreading rate (cm yr ⁻¹)
AA	2.10	I	3.40
BB	2.17	J	3.64
CC	2.07	K	3.86
DD	2.13	L	3.92
EE	2.59	M	3.98
FF	2.74	N	4.24
A	3.00	N ₁	3.17
B	2.94	N ₂	3.32
C	3.05	N ₃	2.58
D	3.08	N ₄	2.76
E	3.34	O	2.91
F	3.49	P	2.97
G	3.49	Q	2.95
H	3.17	R	3.25

as a function of latitude. This change with latitude could not be caused solely by longitudinal convergence.

It is evident from Fig. 4 and Table 1 that the spreading rate for the southernmost profile, R, is 3.25 cm yr^{-1} and that the rate decreases almost uniformly in a northerly direction through profile N_3 , where the spreading rate is 2.58 cm yr^{-1} . At the 29th parallel the spreading rate increases sharply to 4.24 cm yr^{-1} for profile N. Although profiles N_1 and N_2 provide evidence for this increase they do not show its nature or mode because the rates do not increase uniformly with latitude. This rapid increase in spreading rate occurs between $28^\circ 30' \text{ N}$ and $29^\circ 00' \text{ N}$ at the latitude of Guadalupe Island and we see from Fig. 3 that anomalies 5A to 5D are offset at this latitude. Anomalies 6 and 6A show no apparent offset, however. If the

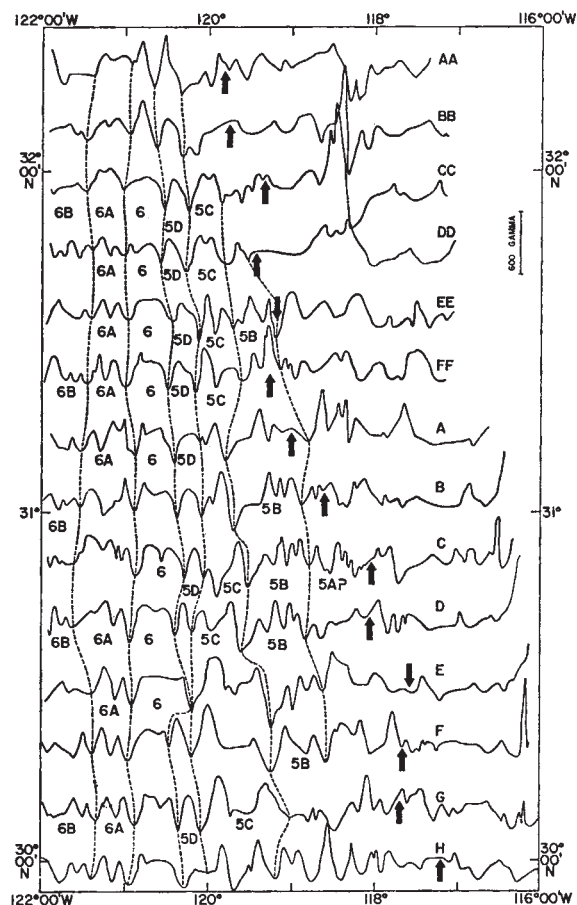


Fig. 2 Residual magnetic profiles. Solid arrows indicate where profile crossed the 1,000 fathom contour.

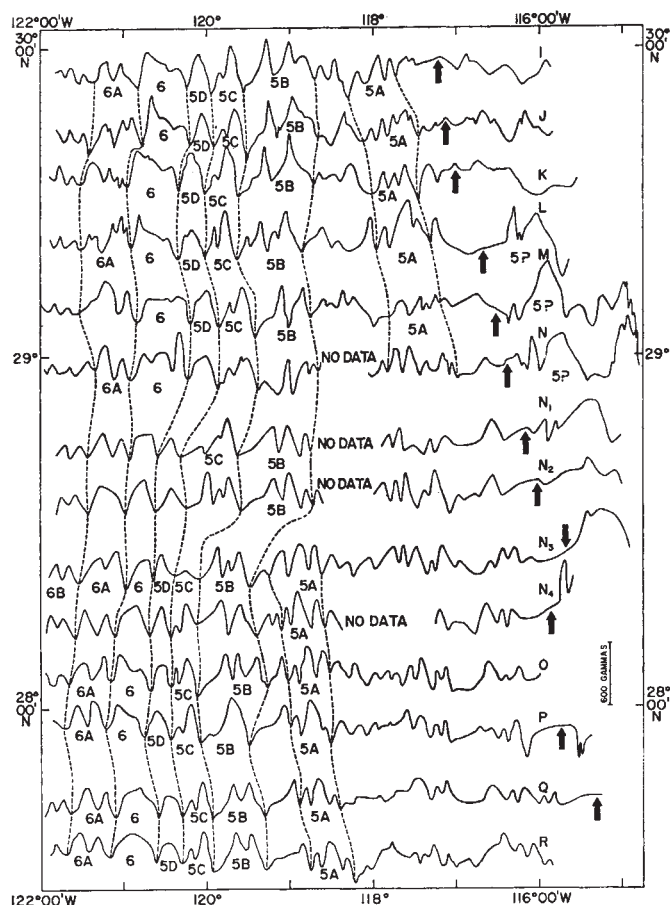


Fig. 3 Residual magnetic profiles. Solid arrows indicate where profile crossed the 1,000 fathom contour.

offset of anomalies 5A to 5D results from a transform fault then this fault must have started during the Miocene (about 20 million years ago). After profile N the spreading rate decreases almost uniformly once again to the northernmost profile AA.

The abrupt change in spreading rate at $28^\circ 45' \text{ N}$ no doubt indicates that there were two different ridge segments displaced by a transform fault and having two different spreading rates. It would seem that about 20 m.y. BP two segments of the East Pacific Rise, which had previously been spreading at a constant rate began to spread at differing rates, thereby producing a transform fault just south of Guadalupe Island. Perhaps the cause of this transform fault can be related to the approach of the North American continental plate from the east.

The time at which the North American continental plate

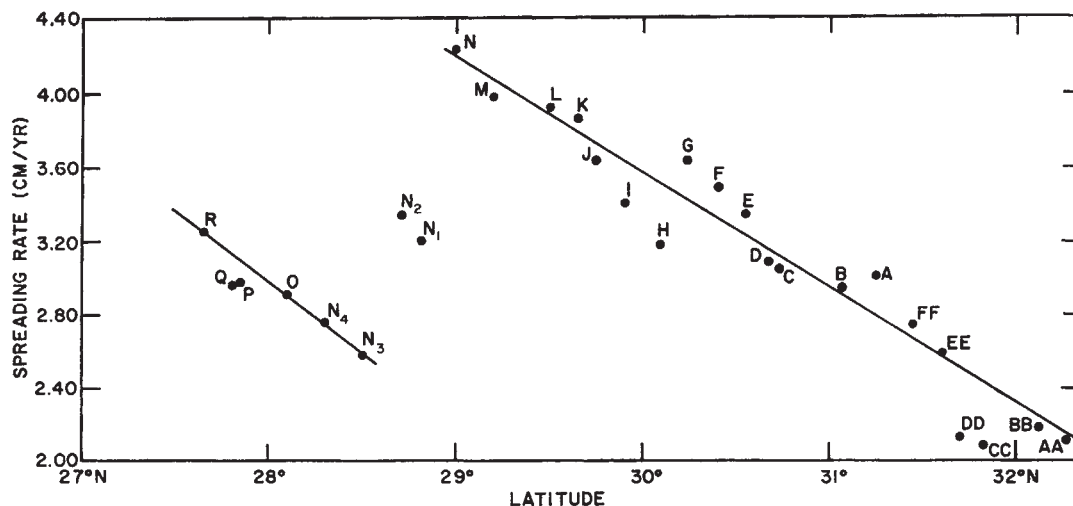


Fig. 4 Graph of spreading rate against latitude as determined from Figs. 2 and 3.

overrode the East Pacific Rise can be determined by noting the age of the youngest identifiable magnetic anomaly against the North American continental margin. It can be seen from Figs. 2 and 3 that along each profile the youngest clearly identifiable anomaly varies from the north to the south. Along profile AA anomaly 5D is the youngest and at profile C anomaly 5A can probably be identified for the first time. The latter is the youngest clearly identifiable magnetic anomaly observed off the west coast of Baja California. Anomaly 5 has, however, been tenuously identified along profiles L, M and N and if it is indeed present then it exists within the 1,000 fathom contour, the location of which is marked by the solid arrow on each profile. If we conclude, for the sake of discussion, that the youngest identifiable anomaly is number 5A, then the indication is that the nascent East Pacific Rise was in existence during the early Pliocene and that the North American continental plate did not override the ridge until some time later than this.

We note, after comparison of Fig. 3 with Fig. 3 of Chase *et al.*⁵, that the entire anomaly sequence (anomalies 5A to 6) has been displaced about 180 km to the left at 27° N. This displacement is not really unusual when one realizes that the Shirley Trough is located along this displacement. Atwater and Menard⁸ show this anomaly sequence offset and indicate that the Shirley Trough is part of the Molokai fracture zone.

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Creep Movements in Low Gradient Clay Slopes since the Late Glacial

SEVERAL measurements of rates of soil creep have been made (for example, refs. 1–4), and the longest continuous period for which movements have been reported is 4 yr (ref. 2). Movements have generally only been detected in the 0.5 m layer just beneath the ground surface, though deeper displacements are recorded⁴. Two observations which seem to give a measure of the total soil creep over a period of 10,000 yr and to a depth of 1.5 m below ground level are of considerable interest.

The largest component of downslope creep movement is thought to be due to seasonal changes in soil water content which result in expansion perpendicular to the ground surface on wetting, followed by preferential downslope shrinkage on drying^{1,3,5}. This mechanism is probably of particular importance in slopes of cohesive soil.

The creep observations reported here relate to two sites in the east Midlands. At the first, near Uppingham, Rutland, two trial pits were excavated during August–September 1970 in the lower half of a fairly uniform 4° slope of Lias clay of south-west aspect. The upper pit (No. 1) showed 0.7 m of head⁶ (liquid limit, LL, 71%; plastic limit, PL, 29%; natural water content, w_{nat} 24%) overlying Upper Lias Clay (LL 63%, PL 29%, w_{nat} 28%) whereas the lower pit (No. 2), 130 m further

downslope, showed 0.5 m of head (LL 60%, PL 22%, w_{nat} 21%) over Lias clay (LL 76%, PL 27%, w_{nat} 27%) near the Upper/Middle Lias boundary.

Seasonal variations in water content and the ground water table are not known at this site, but an estimate of the likely seasonal variations is given by measurements at a similar site, near Barrowden, Rutland (5° slope; south-east aspect; 0.6 m of head over Upper Lias Clay of LL 62%, PL 31%). Between December 1969 and September 1970 the average soil water content to a depth of 1.5 m in the Lias at Barrowden decreased from 35% to 29% and the water table fell from 0.7 m to 2.1 m below ground level.

A feature of both trial pits was a polished shear surface underlying the head deposit. Shear surfaces such as these are produced by the process of landsliding which only occurs on slopes steeper than 8.5° (refs. 7 and 8) in present climatic conditions in the Lias clay of this area. Slopes greater than 8° are necessary in the more plastic London Clay⁹.

Similar shear surfaces have been recorded in both southern England¹⁰ and Northamptonshire¹¹ on slopes flatter than the Critical Landsliding Slope. In both cases shear surface formation has been ascribed to periglacial conditions, because it is thought that the necessary high pore-water pressure can be generated only in such an extreme environment. The minimum age for the shear surfaces reported here may therefore be regarded as about 10,000 yr, dating back at least to zone III of the Late Glacial.

The trial pits also had seasonal shrinkage cracks, with an average spacing (in section) of 0.2 m. These cracks extended from beneath the ploughed layer (at a depth of 0.3 m) to at least 1.4 m below ground level and formed polygonal columns of soil; they all curved downslope and were almost vertical at depth although showing increased displacement from the vertical nearer the ground surface.

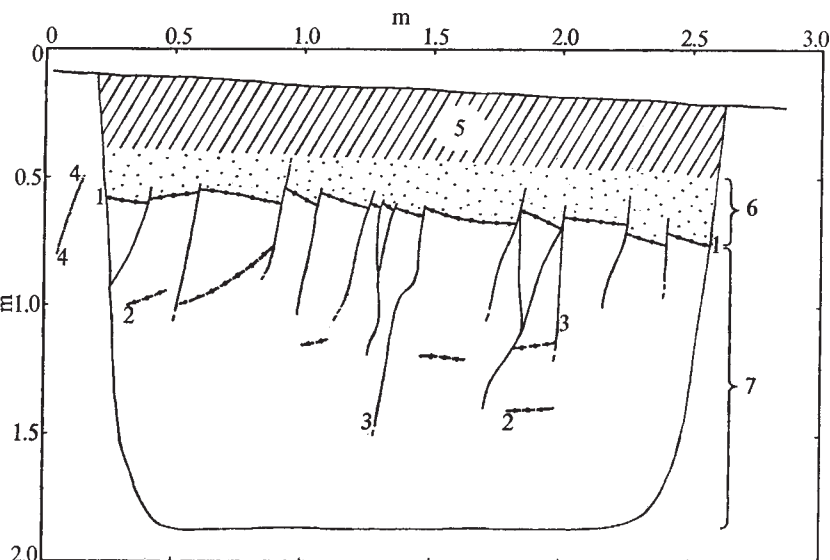
In trial pit No. 2 the shear surface was displaced, or faulted, an average of 25 mm at each shrinkage crack by the downslope deformation of the polygonal soil columns formed between the cracks. The section in the trial pit was logged to an accuracy of about ± 5 mm, and is shown in Fig. 1. The downslope curvature of the shrinkage cracks seems to be compatible with the faulted displacements of the shear surface. It is therefore concluded that the downslope displacement of the shrinkage cracks postdates the formation of the shear surface and consequently provides a measure of the creep movements since the Late Glacial.

The trial pits also suggest an origin for the isolated slickensided surfaces seen in cohesive soils on slopes at shallow depths. They were seen to be subhorizontal in the pits and to extend no further in plan than the cracks bounding the polygonal soil columns. In section it seems that they represent slight horizontal shear displacements arising from the inability of one soil column to sustain the loading imposed by the soil column immediately upslope. Such a process could lead to a progressive loss of strength on steeper slopes and ultimately to landslide movements.

Fig. 1 shows that in trial pit No. 2 the maximum horizontal component of creep movement beneath the ploughed layer was probably about 0.4 m if the shrinkage cracks were originally vertical, and about 0.3 m if the cracks were formed at right angles to the ground surface. Similar movements are suggested by shrinkage cracks seen in trial pit No. 1 (130 m up the slope), and the average inclination of these cracks is shown at the appropriate depth in Fig. 1.

The second observation with which this communication is concerned was provided by a sewer trench just north of Wellingborough, Northamptonshire. The trench exposed a section, parallel to the contours, of a uniform slope of about 1.5° and northerly aspect; this gradient was maintained for 130 m upslope and 50 m downslope of the trench. The section exposed up to 0.9 m of head (LL 56%, PL 29%, w_{nat} 24%) over Upper Lias Clay (LL 61%, PL 28%, w_{nat} 25%) and, in spite of the very shallow angle of the slope, extensive shear

Fig. 1 Uppingham trial pit (No. 2) section showing displacement of Late Glacial shear surface by downslope movement of seasonal shrinkage cracks. 1-1, Shear surface; 2, minor slickensided surfaces (several); 3, shrinkage cracks (several); 4-4, average inclination of shrinkage cracks in pit (No. 1) 130 m upslope, plotted at appropriate depth; 5, brown loamy top soil with Bunter type pebbles and limestone fragments, and sharp lower boundary as a result of ploughing; 6, yellow-brown sandy clay with various erratics; 7, mottled brown/blue-grey silty clay with less weathered lumps of silty clay up to 30 mm becoming frequent toward base of pit (*in situ* Upper or Middle Lias).



surfaces, striated in a downslope direction, were present in the head. These shear surfaces, as in trial pit No. 2 at Uppingham, were also displaced by shrinkage cracks which curved downslope. The downslope curvature of several of these cracks was recorded, though the exposure did not permit detailed logging as in the Uppingham trial pit. The apparent maximum downslope movement observed was 0.22 m just under a 0.23 m thick ploughed layer; this shrinkage crack became vertical 1.01 m below ground level, and had a maximum depth of 1.07 m.

The maximum rates of creep movement implied by the downslope movement of the shrinkage cracks at the two sites are plotted in Fig. 2. It is thought that the maximum crack displacements are those most likely to represent creep since the Late Glacial because those cracks indicating smaller movements may well have been formed at a later date. The creep rates have been calculated assuming that the base of

the crack has always remained stationary, and that the deformation took place over a period of 10,000 yr. At depths around 0.5 m the rates thus calculated agree well with previous short term observations^{2,3} even though the Lias clay slopes are very much flatter.

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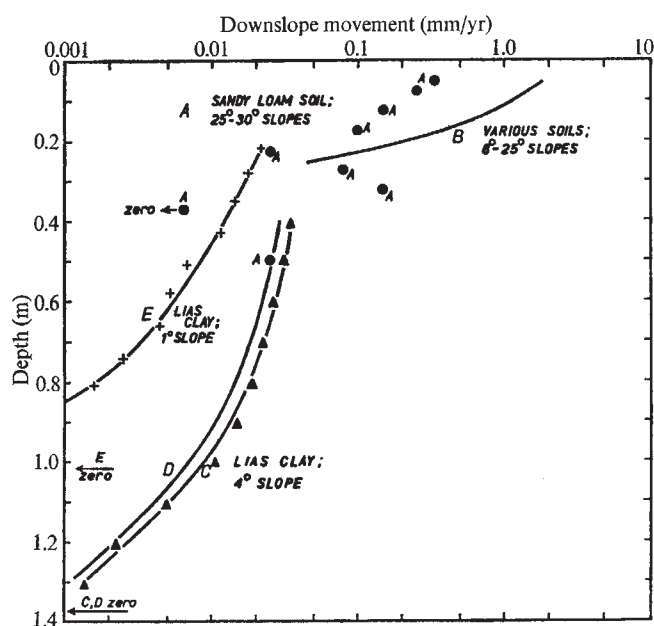


Fig. 2 Rates of downslope creep movements. Points A are plotted from Young²; B is the average curve obtained by Kirkby³ for several soil types and a range of slope angles; curves C and D are the upper envelope of creep rates for the shrinkage cracks of trial pit No. 2; assuming the cracks to have formed respectively vertically and perpendicular to the slope; curve E is the creep rate for the shrinkage crack showing the maximum observed displacement from the vertical at the Wellingborough site.

Aleutian Enigma: a Clue to Transformation in Time

THE current concepts of plate tectonics took shape when Wilson¹ expounded his concept of transforms. He discussed the relationships in space of the three global tectonic elements (ridges, arcs and great faults) which constitute the present network of mobile belts and delineate crustal plates. He suggested that any one of these elements is transformed at its apparent geographic termination into one of the other two, and he termed the junction "a transform". McKenzie and Morgan² have recently written: "There are two main reasons why plate tectonics does not yet provide a complete theory of global tectonics. The first is that the mechanism by which the motions are maintained is still unknown. . . . The other is that the original ideas only apply to motions at present taking place, and are not concerned with either the slow evolution of plate boundaries or with changes in their relative motion through geological time". This article, like that of McKenzie and Morgan, is concerned with the relationships of global tectonic elements in time.

In terms of plate tectonics the Pacific Ocean marks the site of a great crustal (or lithospheric) plate which is at present

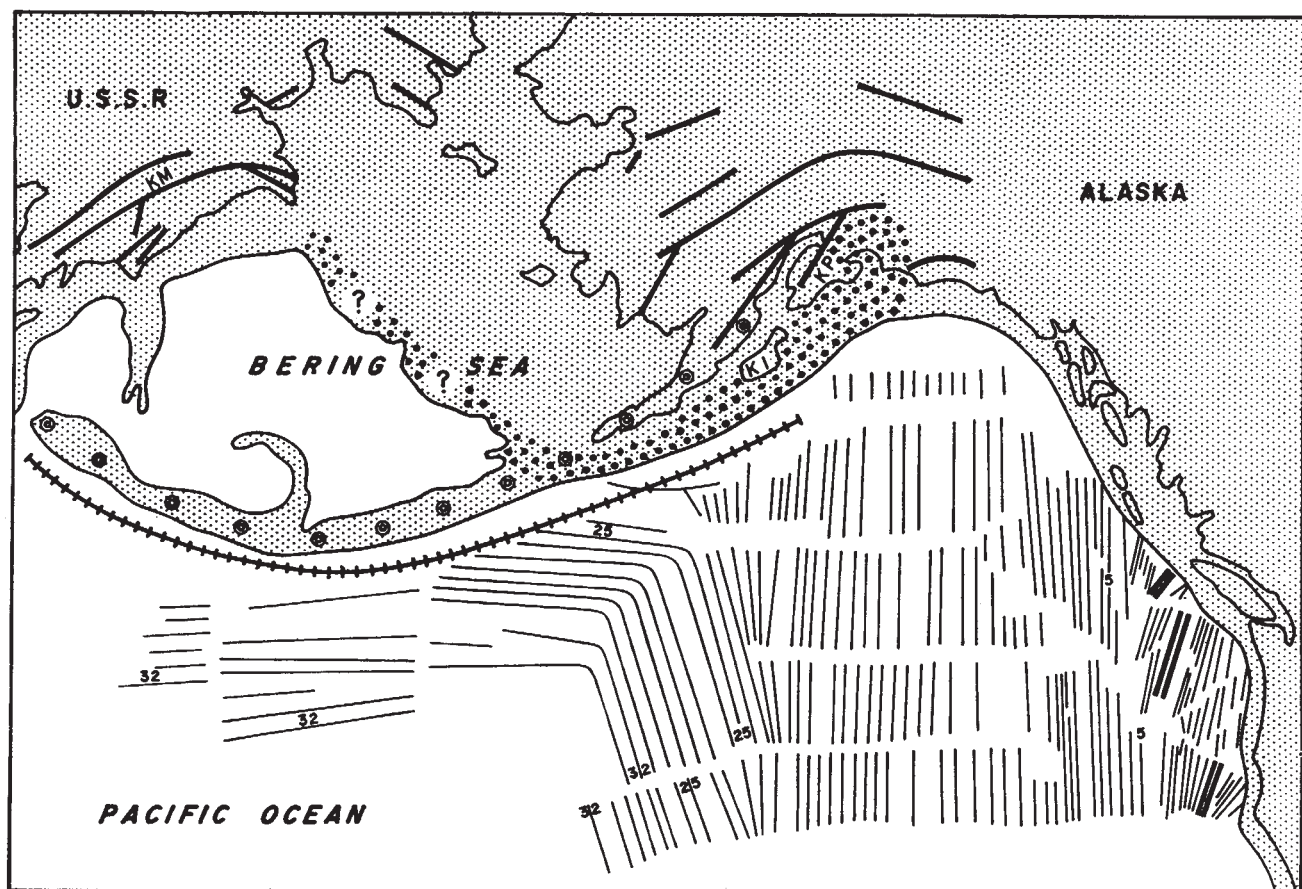


Fig. 1 Gross characteristics of northern Pacific seafloor and continental margin. Seafloor unshaded with northern extension of East Pacific Rise shown by thick double lines, Aleutian Trench by cross-hatched line, and magnetic lineations by thin single lines. Continent and Aleutian Arc, delineated by 2,000 m contour, shaded, with Jurassic to Eocene continental rise shown by stippling, Eocene to Recent volcanic arc by double circles, and principal faults by thick single lines.

accreting along its southern and eastern perimeter at the crest of the East Pacific Rise and being consumed at the island arcs which mark its northern and western perimeter^{3,4}. Few geologists would now reject the hypothesis of generation of crustal material along the axes of oceanic rises and ridges. But there is no consensus on the significance of trenches and island arcs. Seismological data can be interpreted in a manner consistent with the notion of trenches as sinks⁴, but magnetic data, on which plate tectonics so largely rest, are proving more refractory.

The North-East Pacific clearly provides a testing ground for the hypothesis under discussion, for in terms of this hypothesis the Pacific plate should here be moving from the northern extension of the East Pacific Rise towards the Aleutian Trench (Fig. 1). A concept of simple crustal transfer predicts that oceanic crust will become progressively older from source to sink, and it was anticipated that mapping of magnetic anomalies in the North-East Pacific would reveal such a pattern. Yet the contrary has proved the case, for approaching the Aleutian Trench the north-south magnetic anomalies paralleling the East Pacific Rise turn west (Fig. 1), forming the Great Magnetic Bight. Consequently the age of the oceanic crust appears not to increase, but to decrease toward the trench: "in this one area, where magnetic anomalies are well documented as being adjacent and subparallel to a deep-sea trench, the inferred chronology of the anomalies is opposite to what would be predicted for seafloor spreading . . ."⁵.

Pitman and Hayes⁶ have tentatively proposed that the pattern of magnetic anomalies south of the Aleutian Trench was generated by an east-west ridge segment which migrated northwards as it spread until it plunged into the Aleutian Trench where its activity was stifled. For Heirtzler⁷ this

anomaly pattern is "one of the most awkward sticking points in the theory" (that is, the theory of seafloor spreading with trenches as sinks).

It seems to me that the Aleutian enigma calls for a review of the assumptions of seafloor spreading, source to sink. One common, if implicit, assumption is that the present character of plate boundaries has been maintained from the time of their inception. I wish to explore the possibility that in time divergent plate boundaries may be transformed into convergent boundaries; that is, that in time sources may become sinks.

I shall assume that at the time of anomaly 32 (the oldest of the extensively mapped magnetic anomalies in the North-East Pacific) the eastern and northern perimeter of the Pacific plate was accreting along a boundary of rectangular form. In time a pattern of magnetic anomalies like that shown by the north-east sector of the Pacific plate would be generated (Fig. 2a). I shall further assume that at some time after the generation of the youngest anomaly now roughly parallel to the Aleutians (anomaly 25), the northern perimeter ceased to accrete and became instead a zone of plate convergence. Then overriding of the Pacific crustal plate by the plate to its north might give a formerly accreting margin the character of a zone of consumption or crustal sink (Fig. 2b). The geometrically simplest model for the generation of the present characteristics of the north-east sector of the Pacific plate would have a prolonged phase of plate accretion (Fig. 2a), followed by a phase of rapid plate consumption along the northern perimeter (Fig. 2b). A model more consistent with the history of the Aleutian arc and northern Pacific continental margin would involve two phases of more nearly equal duration: the first marked by simple plate accretion (Fig. 2c); the second by plate consumption along the northern perimeter and con-

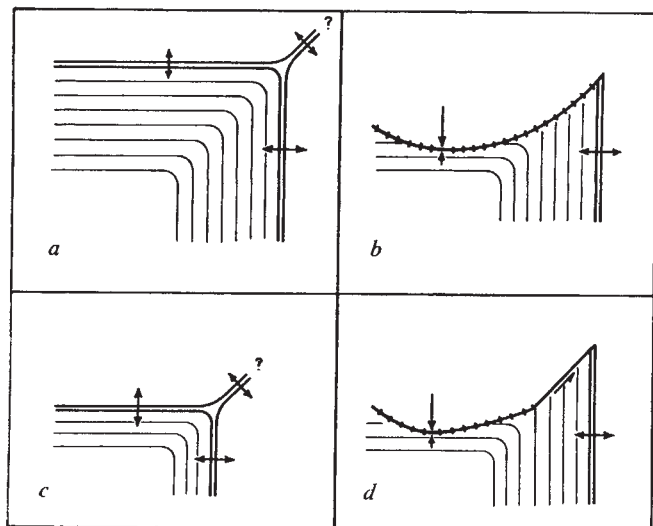


Fig. 2 Evolution of Pacific plate. Symbols as in Fig. 1 with addition of transform fault shown by thick single line. See text for description.

tinuing plate accretion along the eastern perimeter, the active zones connected by a ridge to arc transform fault (Fig. 2d).

The crucial event embodied in this hypothesis is a transformation in the character of the northern perimeter of the Pacific plate—from a zone of plate divergence or source, to a zone of plate convergence or sink. Since the hypothesis attributes the generation of the east-west trending magnetic anomalies of the north Pacific to the prior phase, this crucial event must have occurred after the formation of the youngest of these anomalies (anomaly 25), tentatively dated earliest Tertiary (63 m.y.)⁸. Is there any evidence for such an event along the northern shores of the Pacific?

The Pacific continental shelf of Alaska is underlain by a great accumulation of slate, greywacke and basalt pillow lava which rises above sea level to form the greater part of the Kenai Peninsula and Kodiak Island (KP and KI, Fig. 1)⁹⁻¹². The wholly marine strata of this Alaskan "slate and greywacke belt" are of turbidite facies and were deposited on an unknown floor. Though poorly fossiliferous, they appear to range in age from Jurassic to Eocene¹². They are intruded by granodioritic plutons, dated earliest Tertiary (56-64 m.y.) in

the Shumagin Islands, and overlain unconformably on Kodiak Island by non-marine strata containing dioritic debris and a fossil flora of Oligocene age⁹. Burk⁹ suggests that these strata accumulated as a late Mesozoic continental rise or trench infilling which was intruded and uplifted to form the present Pacific continental shelf in the early Tertiary.

The outer continental shelf of Alaska in the Bering Sea is shown by a recent seismic reflexion investigation¹³ to be underlain by an accumulation of strata as much as 1,500 m thick, resting on an "acoustic basement". Dredging has recovered diatomaceous siltstone and tuffaceous sandstone with mid-Tertiary fossils from the overlying strata, and siltstone and mudstone with late Cretaceous foraminifera from the basement¹³. Seismic reflexion profiles across the Bering Sea shelf suggest that the locally irregular surface of the acoustic basement is continuous with an areally extensive unconformity separating rocks of Mesozoic and Tertiary age along the west coast of Alaska. If the surface of the acoustic basement is the regional unconformity it appears to be, then it presumably records an interval of uplift and erosion some time between the late Cretaceous and the middle Tertiary.

Burk noted the lithological similarities between the rocks of the Pacific margin of Alaska and contemporaneous rocks along the western margin of the Bering Sea where what are believed to be bathypelagic volcanic and sedimentary rocks of Cretaceous age occur in northern Kamchatka and the Koryak Mountains (KM, Fig. 1)^{9,14}. He further suggested that the rocks of these regions are linked via the Bering Sea continental margin of Alaska. The rocks of the acoustic basement defined by Scholl and others¹⁴ could well prove to be this link.

The islands of the Aleutian arc consist of dominantly andesitic volcanic rocks, their sedimentary derivatives, and quartz-dioritic plutons¹⁵. With the exception of a small isolated exposure of late Paleozoic rocks on Adak Island, the oldest fossils reported from the Aleutians are early Oligocene⁹. The volcanic arc of the Aleutians extends onto the Alaskan continental shelf as the Alaska Peninsula where andesitic volcanism has dominated sedimentation from the Eocene to the present⁹. The Aleutian arc stands in a truly oceanic environment, though the oceanic crust to the north is depressed beneath sediments 3 km thick¹⁶.

Thus it seems probable that the early Tertiary witnessed two major events along the northern margin of the Pacific. First

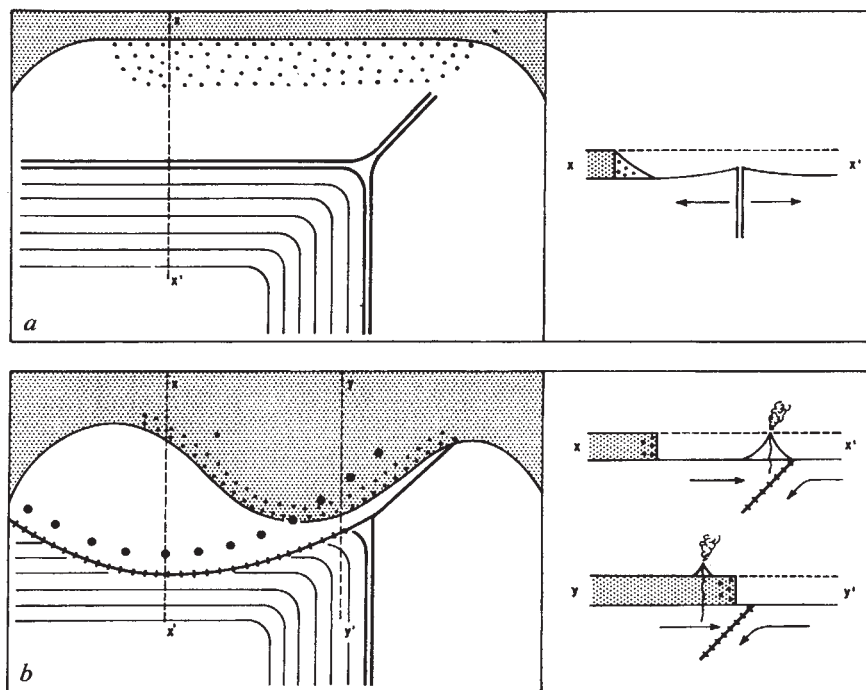


Fig. 3 Postulated early Tertiary rise to arc transformation at the northern margin of the Pacific plate: *a*, just before transformation; *b*, just after transformation. Symbols as in Figs. 1 and 2.

there was uplift and erosion of a probable late Mesozoic continental rise along the Pacific margin of Alaska in the late Eocene or early Oligocene; and of a possible late Mesozoic continental rise along the Bering Sea margin of Alaska some time between the late Cretaceous and middle Tertiary. Second, there was initiation of the Aleutian arc in the Eocene.

I suggest that these two events may record my postulated early Tertiary transformation in the character of the northern perimeter of the Pacific plate—from a zone of plate divergence to a zone of plate convergence. An integrated model of this gross aspect of this transformation as it may have affected seafloor and continent is presented in Fig. 3.

While the magnetic anomaly pattern of the North-East Pacific is grossly rectangular, as depicted in Figs. 2 and 3, it shows significant departures from this pattern in detail (Fig. 1). These take the form of relatively abrupt changes ($\sim 10^\circ$ – 20°) in the trend of magnetic lineations. Two such changes occur in the North-East Pacific, one commencing between anomalies 25 and 23, and one between anomalies 10 (just to the south of Fig. 1) and 5 (refs. 2 and 17). In the southern Pacific there seem to be changes in spreading rate commencing within these intervals⁸, suggesting that these events may have Pacific-wide significance. The time scale of Heirtzler and others⁸ assigns a Paleocene age to anomaly 25. On the other hand, if the postulates of Helsey and Steiner¹⁸ prove correct, the date of this anomaly could be Eocene. In either case the event is of early Tertiary age and may conceivably coincide with the postulated transformation along the northern margin of the Pacific plate.

The tendency of magnetic lineations to parallel the margins of the Pacific plate as they are followed anticlockwise through its north-east sector appears to persist into the north-west sector where as yet undated anomalies trend north-east–south-west, nearly parallel to the Kurile arc¹⁹. Rise to arc transformations may prove a common event in the evolution of the Pacific plate.

I thank R. Cas and J. J. Veevers for reviewing my manuscript; since this article was written my attention has been directed to a paper by Franchetau and others²⁰. From a study of the magnetization of Pacific seamounts they infer a 30° northward movement of the north-east portion of the Pacific plate in the interval between the Upper Cretaceous and the present. While this finding is of great interest, its implications for the model presented here cannot be assessed until similar information is available for the movement of the other tectonic elements which the model incorporates, in particular the plate of which the oceanic Bering Sea is part. It should be stressed that the model I present is concerned solely with the motions of the constituent tectonic elements relative to one another and not with their movements relative to the geographic poles. For a discussion of the motions which can be inferred from seafloor spreading and palaeomagnetic data, see Franchetau and Sclater²¹.

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Observations of a Regular Void Array in High Purity Molybdenum irradiated with 2 MeV Nitrogen Ions

VOIDS in metals, formed as a result of neutron irradiation or particle bombardments, are usually found to be distributed randomly in the lattice. But I have found that voids can take up regular positions in the lattice with respect to each other and demonstrate that the voids form a body-centred-cubic superlattice structure with crystallographic axes identical with those of the molybdenum matrix. The voids in this case were formed as a result of particle irradiations but some observations made on neutron irradiated molybdenum (F. W. Wiffen, private communication) indicate strongly that this same void structure may be present in that case as well.

The molybdenum specimens used were single crystal disks produced from electron beam zone refined material, subsequently annealed near the melting point in high vacuum. This treatment produced crystals of very low dislocation density ($\sim 10^7$ lines/cm²) and high resistivity ratio ($R_{293\text{ K}}/R_{4.2\text{ K}} \sim 6,000$). The irradiations were carried out on a Van de Graaff accelerator producing 2 MeV nitrogen ions, and the specimens were then thinned by electropolishing techniques to view the damage layer in a Philips 'EM 300' electron microscope operating at 100 keV. The specimen discussed here was irradiated at 870° C to a dose of 7×10^{17} N⁺ ions/cm².

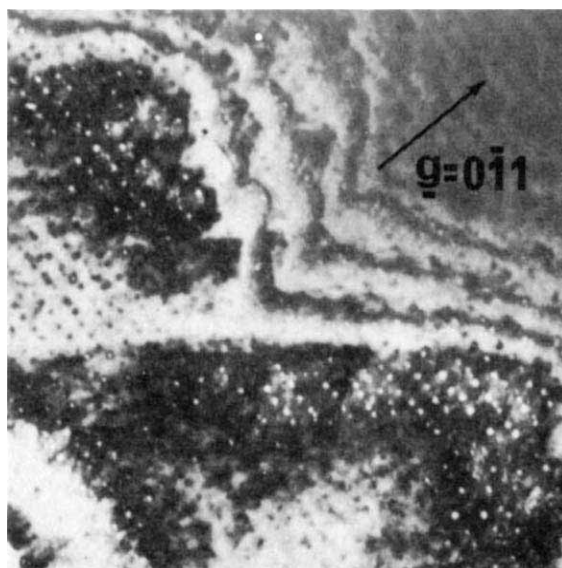


Fig. 1 Micrograph showing alignment of the void positions in the foil. Diffracting conditions: $z=[155]$, $g=0\bar{1}1$, $s=0$.

The appearance of the voids is shown in Fig. 1, for which the diffracting conditions were $z = [155]$, $g = 011$ and $s = 0$. The regularity of the voids can be seen as an alignment either

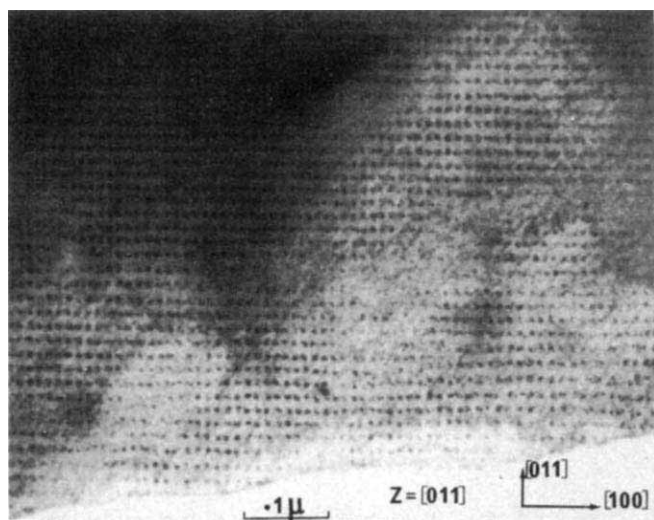


Fig. 2 Foil tilted to $z=[011]$ bringing up more than one direction of void alignment.

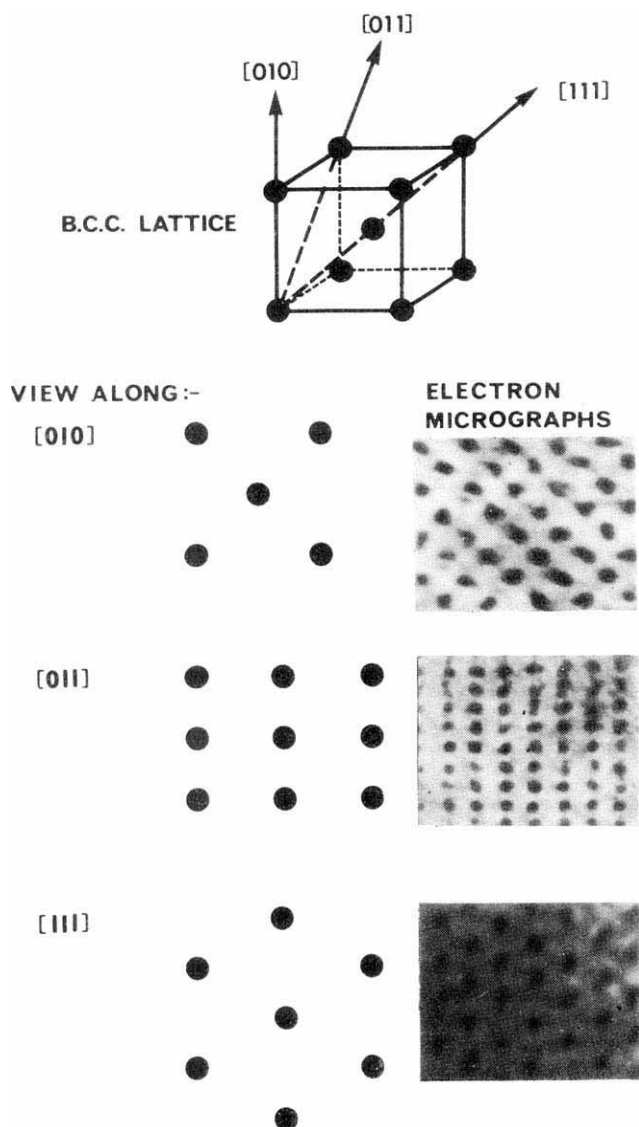


Fig. 3 The projections of a b.c.c. lattice along the $[011]$, $[010]$ and $[111]$ directions together with micrographs showing the projections of the void lattice along the same directions.

in the $0\bar{1}1$ plane or in some direction contained in this plane. Tilting the foil to a perfect orientation $z = [011]$, and choosing diffracting conditions to avoid the thickness fringes apparent in Fig. 1, shows the void array even more convincingly while the appearance of the void row in an orthogonal direction, that is, in the (100) plane, indicates that the array is three dimensional (Fig. 2). The regularity of a projection of a two dimensional array would not depend on orientation. This three dimensionality is also shown by micrographs taken with the foil tilted to $z = [010]$ and $z = [111]$ which demonstrate (Fig. 3) that the image projections satisfy a body-centred-cubic structure. The lattice parameter was measured on this assumption from all three projections and found to be $220 \pm 10 \text{ \AA}$.

The reason for the formation of this void lattice is not clear and, as far as is known, has not been theoretically predicted. Briefly the formation could either be a nucleation phenomenon, where voids are nucleated on an impurity superlattice existing prior to the irradiation, or could be due to interaction between the voids once they are formed causing the voids to climb into "lattice sites" relative to their neighbours, minimizing their free energy by doing so. Because no such interactions can exist between voids in an isotropic lattice the anisotropy of the molybdenum lattice could be an important factor in this mechanism.

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Simplification of the Proton Magnetic Resonance Spectrum of Ribonuclease by Difference Spectroscopy

NATIVE proteins in solution usually give rise to nuclear magnetic resonance (NMR) spectra containing broad overlapping bands¹⁻⁵. These bands contain a great deal of useful information, most of which cannot be extracted without some simplification of the spectra. Selective deuteration is one method for reducing the complexity of macromolecular NMR spectra^{6,7}, but the production of deuterated proteins is not always feasible. NMR difference spectroscopy is simpler, relying on the principle of selective perturbation (by means of change of solvent, pH and so on) of only one or several types of proton resonances in the spectrum. This technique has been used previously to examine differences between the spectra of bovine and porcine insulin⁸ and to study the binding of Co(II) to the carboxyl groups of gelatine (reported by P. I. Rose at IUPAC symposium on macromolecular chemistry, Toronto, 1968).

We have used NMR difference spectroscopy to separate the C-4 imidazole peaks of ribonuclease A from overlapping resonances. Another application⁹ is the observation of protons attached to nitrogen in the side chains of lysine and arginine and amide protons, all of which exchange fairly slowly with the solvent between pH 2 and 7 (ref. 10).

The realization that the C-2 proton resonances of the histidine residues of proteins are well separated from the main aromatic envelope^{2,3} and also that they undergo a large chemical shift on titration (in histidine itself¹¹) led Bradbury and Scheraga⁴ to obtain the first NMR results (at 60 MHz) on the pK of the histidine residues in ribonuclease A. This work was repeated by Meadows *et al.*¹² at 100 MHz and extended to the assignment of the four C-2 proton resonances to the various histidine residues in the molecule¹³. The assignment is satisfactory as far as ribonuclease S is concerned, but its extension to

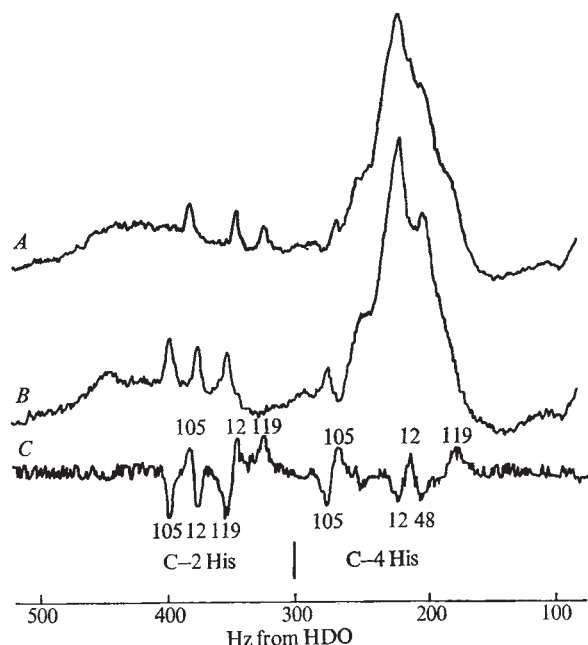


Fig. 1 NMR spectra at 100 MHz and 34° C of 10% solutions in D₂O of Worthington ribonuclease A. *pH* values are meter readings uncorrected for deuterium isotope effects and were adjusted with 6 M DCl-HCl or NaOD. Each spectrum is the average of thirty scans downfield from HDO, of the aromatic region obtained at a sweep rate of 5 Hz/s on a Varian HA-100 spectrometer. A, *pH* 5.96; B, *pH* 5.35; C, difference spectrum = A-B. The numbers refer to proton resonances of the histidine residues in the molecule as previously assigned¹³.

ribonuclease A rests on the assumption that the titration curves for His 12 and His 119 both move to lower *pH* values by about the same extent in going from ribonuclease S to ribonuclease A; that is, the *pK* of His 12 falls from 6.7 to 6.2 and His 119 from 6.3 to 5.8. The alternative possibility is that the *pK* of His 12 drops from 6.7 to 5.8 and that of His 119 from 6.3 to 6.2. A correct assignment is obviously essential in the development of theories of action of the enzyme based on NMR studies¹⁴⁻¹⁶. A study of the C-4 resonances of the histidines of ribonuclease A may be useful to resolve the experimental differences between the normal S-shaped titration curves obtained by Jardetzky and co-workers^{12,14} and the unusual "modified" sigmoidal curves obtained by Rüterjans and Witzel¹⁶.

In ribonuclease A only one of the C-4 proton resonances of histidine—that arising from His 105 (ref. 12)—can be distinguished in the normal NMR spectrum from overlapping aromatic resonances of phenylalanine and tyrosine. Observation of the four C-4 resonances, however, can be achieved by NMR difference spectroscopy, since their chemical shifts are *pH*-dependent, whereas the aromatic proton resonances are *pH*-independent between about 4.5 and 7.5. Thus, Fig. 1 shows the NMR spectra of the aromatic region of ribonuclease A at *pH* 5.96 and 5.35, together with the difference spectrum obtained by subtracting one from the other. A PDP-8/S computer was used on-line with the NMR spectrometer to increase the signal to noise ratio by averaging spectra. Each spectrum was stored on punched tape and could be read back into the computer for subsequent determination of difference spectra. The difference spectrum in Fig. 1 clearly separates those peaks whose chemical shifts are dependent on *pH* from those which are not. Several subtractions were usually required for each spectrum, because of occasional cancellation of coincident peaks. For example, in Fig. 1 the C-4 peak of His 48 at *pH* 5.96 has the same chemical shift as the C-4 peak of His 119 at *pH* 5.35, and so these two peaks are absent in the difference spectrum. To reveal these peaks, subtractions were necessary from spectra at other *pH* values.

The titration curves for the C-2 and C-4 proton resonances are given in Figs. 2 and 3 and the apparent *pK* values equal the *pH* values of the mid-points of the total titration curves. The same apparent *pK* values are obtained from both the C-2 and C-4 curves—5.2, 5.8 and 6.4. These agree with those obtained previously at low ionic strength—5.1, 5.6 and 6.4 (ref. 16)—which have been assigned to His 119, 12 and 105 respectively¹³. We have interpreted our results on the basis of this assignment. The resonance corresponding to the histidine residue with lowest *pK* moves even farther downfield in Fig. 2 as the *pH* is reduced below 4. Such behaviour suggests the proximity of a carboxyl group, the titration of which is being reflected in the curve for the C-2 histidine peak. Because X-ray evidence¹⁷ indicates that Asp 121 is closer to His 119 than to His 12, this observation provides supporting evidence for the assignment of His 119 to the curve with lowest *pK*.

Fig. 2 shows that the chemical shifts at high and low *pH* of the various C-2 protons are very similar (with the exception of His 48 at low *pH*) whereas those of the various C-4 protons (Fig. 3) are much more variable. This may be simply due to the closer proximity of the C-4 protons to nearest neighbours in the polypeptide chain than occurs with the C-2 protons, hence causing the greater variability of the magnetic environment of the former.

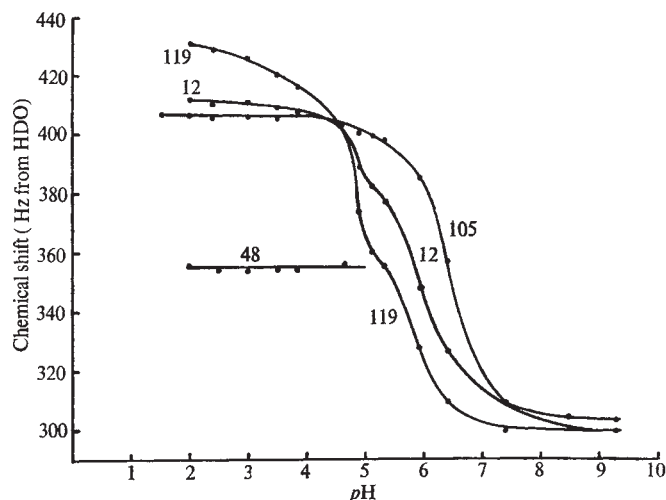


Fig. 2 Histidine C-2 proton titration curves of ribonuclease A. The numbers refer to the residues in ribonuclease A as previously assigned¹³.

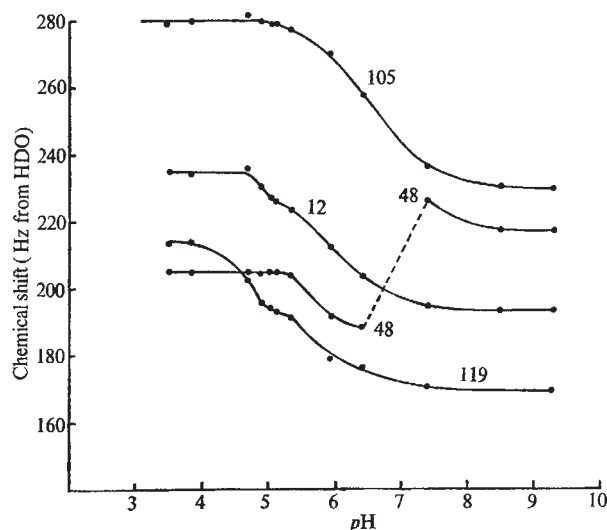


Fig. 3 Histidine C-4 proton titration curves of ribonuclease A. The numbers represent assignments of resonances to specific residues in the protein as described in the text.

The titration curves for the C-2 and C-4 protons of His 12 and His 119 at low ionic strength in Figs. 2 and 3 both show similar deviations from sigmoidal shape, which also agree quite closely with those previously observed for the C-2 protons at low ionic strength and in 0.2 M NaCl (ref. 16). These deviations were not observed by Jardetzky and coworkers (refs. 12 and 18) and we cannot reconcile the discrepancy, for all the normal parameters of source of enzyme (Worthington) temperature (30°–34° C) and solution conditions seem to be almost identical. Because the deviations occur both at low ionic strength and also in 0.2 M NaCl it seems unlikely that they are the consequence of an electrostatic interaction between the imidazole rings. The deviations are removed in the presence of inhibitors such as cytidine-2'-phosphate (ref. 16) or by use of Sigma ribonuclease A, which is known to contain sulphate ion⁹. X-ray diffraction studies of ribonuclease S, which was crystallized in the presence of sulphate ion, showed that a sulphate ion was situated between the two imidazole groups at the active site (personal communication from H. W. Wyckoff). Thus, the presence of sulphate or an inhibitor would have the effect of separating the imidazole rings and also removes the observed deviations from sigmoidal behaviour of the titration curves. This observation is therefore consistent with the explanation for the deviations in terms of a hydrogen bond between the imidazole rings which is removed when both rings are protonated¹⁶.

In confirmation of other work^{16,18} it is found that the C-2 proton resonance of His 48 is not visible at pH > 6 (Fig. 2), although the C-4 resonance is visible throughout the titration range. The apparent discontinuity shown by the dotted line in Fig. 3 is indicative of a limited conformational change; for example, His 48 may interact with Asp 14 at low pH, but with Tyr 25 at high pH (ref. 17). The absence of the C-2 peak at pH > 6 has been attributed to extreme broadening arising from exchange of the imidazole group between different environments at an appropriate rate^{16,18}. Any such exchange, however, should have the same rate for both the C-2 and C-4 protons and hence broaden both peaks. A more likely explanation is that broadening is produced by the C-2 proton coming into close proximity with a proton on another chemical group in the conformation adopted at high pH (ref. 19), but this will be discussed in more detail later.

The unusual behaviour of His 48 illustrates the value of examining both C-4 and C-2 resonances in titration studies of histidines in proteins. NMR difference spectroscopy is clearly very useful in this respect and will find use in other situations⁹, in which the presence or chemical shift of a peak is dependent on any parameter in a manner different from that of the overlapping peaks.

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BIOLOGICAL SCIENCES

Humerus of *Dryopithecus* from Saint Gaudens, France

IN 1856 Édouard Lartet described a hominoid humerus which had been found at the same time and place as the type mandibular fragments of *Dryopithecus fontani*¹. This was the first recording of a fossil great ape. The site of this classic find was a brickworks in Miocene marly clays at the base of a wooded hill or plateau on which the village of Saint Gaudens (Haute Garonne), France, is situated.

The first partial mandible, as well as two others, and isolated teeth later found at the same site have been extensively discussed^{2–5}. On the contrary, the partial left humerus then recovered has never been thoroughly analysed, presumably because both epiphyseal regions are missing. As one of only four described postcranial bones of extinct Eurasian great apes, this humerus is of great significance to considerations of the evolution of hominoid locomotion. As far as we are aware the morphology of this bone has only been commented on briefly by Lartet¹ and by Le Gros Clark and Leakey⁶.

Reference of the specimen to *Dryopithecus fontani* was assumed by Lartet¹, who remarked: "On a trouvé en même temps un humerus . . ." Nevertheless, the probability, although remote, that this humerus could have belonged to some other hominoid should be considered. First, no primate other than *Dryopithecus fontani* has been discovered in the Saint Gaudens clays. Moreover, five different individual finds of teeth or jaws, all clearly referable to *D. fontani*, have been made at what appeared to Harlé⁴ to be the same 385 m level of the cliff. From these finds Harlé concluded that this ape was common at the site. Furthermore, no teeth of great apes which cannot be referred to genus *Dryopithecus* have been discovered elsewhere in the European Miocene, although this ape has been found at more than a dozen sites⁷. It seems reasonable therefore to consider the humerus as assignable to *D. fontani*, or, if not to that species, at least to genus *Dryopithecus*.

The age of the Saint Gaudens deposits (on the basis of the contained fauna) seems post-Vindobonian and pre-Pannonian, that is of the late Miocene Sarmatian provincial age. Recent K/Ar determinations made in Europe⁸ indicate the Sarmatian as the period between 12.5 and 14 million years ago.

The ecological setting of Saint Gaudens, as well as that of the late Miocene of Europe generally, suggests a climate which was no warmer than are these latitudes today with floras near Saint Gaudens containing pine, chestnut and oak. A temperate forest of this sort is unlikely to have harboured a principally arboreal ape, for the relatively sharp seasonality of

fruiting and leaf formation would have effectively restricted exclusive arboreal feeding for an animal as large as a chimpanzee. It seems almost requisite therefore that terrestrial foraging for food would have been frequent.

This humeral fragment of *D. fontani* consists of an almost complete diaphysis. Both epiphyses are missing. At its proximal end, the bone has been subject to post-mortem crushing, reducing the anteroposterior and increasing the transverse diameter. At the distal end, the superior half of the olecranon fossa is preserved, although there has been some distortion of the superior margin.

Dimensions of the fossil humerus are as follows (in mm; estimated measurements marked *):

	<i>Dryopithecus fontani</i>	<i>Pan paniscus</i> (AMNH 86857)
Maximum length	*265	245
Biepicondylar breadth	* > 45	46
Midshaft diameter		
Anteroposterior	18.6	17.2
Transverse	20.2	16.8

In overall size and robusticity the fossil closely resembles the pygmy chimpanzee, *Pan paniscus*, although its biepicondylar breadth is relatively a little smaller. The shaft is slightly bowed laterally as in *P. paniscus*; viewed laterally the shaft is straight with a slight anterior curvature in the distal third. The delto-triceps crest is poorly developed, as in *P. paniscus*, and unlike arboreal and terrestrial cercopithecoids. The delto-pectoral crest is similar to that of *P. paniscus*, and unlike those of cercopithecoids. The orientation of the bicipital groove has almost certainly been unaffected by the proximal crushing. The groove faces more anteriorly than laterally; the opposite is the case in cercopithecoids. The orientation of the groove is related to the orientation of the head of the humerus. In cercopithecoids the head is directed posteriorly; in *Pan* and other hominoids the head faces postero-medially, and this torsion is reflected in the more anterior direction of the bicipital groove. Thus, although the head is missing in the fossil, it can be concluded that there was some medial torsion of the humeral head in the Saint Gaudens fossil, and probably about as much as typifies *Pan paniscus*. Unfortunately, it is not possible to estimate how far distally the deltoid insertion reaches.

At the distal end, the lateral epicondylar ridge (supinator crest) is poorly developed, as in hominoids. The posterior part of the shaft lateral to the olecranon fossa faces posteriorly, and is broad and relatively flat as in *Pan*; in cercopithecoids it is narrower, and faces much more laterally. In the fossil, some 40% of the posterior face of the distal extremity lies lateral to the olecranon fossa. In *Pan troglodytes* and in *Pan paniscus* this region occupies between 30% and 40% of the total biepicondylar breadth; in cercopithecoids values fall to between 20% and 30%. This feature reflects the fact that in *Pan* and among other hominoids the capitulum is well developed and clearly separated from the trochlea. The fossil humerus is therefore likely to have resembled hominoids rather than cercopithecoids in the relative size of the capitulum.

In overall morphology the fossil humerus resembles those of hominoids rather than those of cercopithecoids, and among hominoids it is closest in size, gracility, and in morphology to *Pan paniscus*. Presumably the morphological resemblances indicate functional similarities. The torsion of the head, implying a degree of forelimb mobility comparable with that of *Pan* and other hominoids, and the inferred hominoid-like structure of the distal extremity are particularly interesting. Whether or not the humerus is from an arboreal hominoid like the orangutan or a more terrestrial species such as the chimpanzee cannot be determined. The little that is known of the palaeoecology of Saint Gaudens suggests, however, that hominoid species living in late Miocene times in southern France must have been less arboreal than the orangutan.

Whether or not the species concerned was a "knuckle walker" is unknown, although this is definitely possible.

Two other forelimb bones, a partial humerus and ulna, of a large hominoid—probably *Dryopithecus fontani*—are known from Miocene deposits in Europe⁹. These have been described previously as *Austriacopithecus weinfurteri*, and come from Klein Hadersdorf in north Austria⁷. The humerus is larger than the Saint Gaudens specimen, but nevertheless is basically similar in morphology; however, the delto-pectoral crest is better developed in the Austrian specimen, possibly because of the greater overall size of the individual. The ulna is very similar in size and morphology to the same bone in the pygmy chimpanzee. The articular facet for the radius faces laterally as in hominoids, not superiorly as in cercopithecoids. The greater sigmoid notch is smoothly rounded, and the distal border of the notch is not curved back to form a hook-like coronoid process. In both features the fossil resembles the same region of *Pan paniscus* and differs from that of *Pongo pygmaeus* markedly. The olecranon process, although damaged, was relatively short in the Austrian fossil, as is the case for modern hominoids; it resembles that of *Pan paniscus* rather than this structure in *Pongo pygmaeus*. Collectively, these resemblances suggest the possibility that the ulna, at least, comes from a knuckle walker.

It seems very likely that the three forelimb bones discussed here can be assigned to a single species, probably *Dryopithecus fontani*. They provide evidence that at least one European Miocene dryopithecine was not cercopithecoid-like in its forelimb morphology, but closely resembled the similar-sized hominoid *Pan paniscus*, which is a knuckle walker. *D. fontani* may have been a knuckle walker, although the evidence as it stands is not definite.

It has been thought for some time that Miocene hominoids differed post-cranially from living hominoids, resembling instead the cercopithecoid monkeys¹⁰. But careful examination of the postcrania of *Limnopithecus*¹¹ from the east African Miocene and the European fossil *Pliopithecus*⁹ indicates that such non-hominoid structural features as they have are ceboid-like rather than specifically cercopithecoid-like. Those of early Miocene *Dryopithecus* from Africa are basically hominoid-like, although as expected they are more primitive in some features than are any living species (personal communication from A. C. Walker). The late Miocene European forms discussed here are clearly more hominoid-like; however, a possible *D. fontani* femur from the earliest Pliocene deposits at Eppelsheim in Germany differs markedly from *Pan paniscus*. Clearly the dryopithecines were more primitive in overall postcranial anatomy than any living hominoid species.

It needs to be emphasized, however, that the known forelimb material of *Dryopithecus* species differs distinctly from any cercopithecoid, and, at least in the European species, is very similar to the living African pongids.

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Appearance of *Hipparion* in the Tertiary of the Siwalik Hills of North India, Kashmir and West Pakistan

Hipparion species are important markers in faunal correlations. Their appearance is normally taken to define the boundary between the Miocene and Pliocene in continental deposits¹. The genus is thought to have evolved in North America, probably around 12 million years ago², and the spread of early, primitive *Hipparion* species to Eurasia has consequently been presumed to have occurred at this time, although it might have happened earlier if *Hipparion* older than 12 million years is dated in North America. The relative age of the faunas of the classic Siwalik deposits of north-west India and Pakistan is of considerable interest for the dating of the fossil primates *Dryopithecus* and *Ramapithecus*. The age of these primates is important because *Ramapithecus* has been recognized as the earliest probable hominid and it may lie in the direct line of human ancestry.

The Siwalik series has been divided into a number of faunal zones¹. Those which concern us here—proceeding from oldest to youngest—are the Chinji, the Nagri and the Dhok Pathan. The Dhok Pathan is clearly of Pliocene age; the chronological position of beds containing Chinji and Nagri faunas has, however, been a subject of some controversy (see ref. 1 for a discussion of the literature).

For many years it has been accepted that *Hipparion* is first found in Siwalik deposits of Chinji age (see Lewis³ and Colbert¹). Accordingly, some workers have placed both Chinji and Nagri faunas within the Pliocene⁴. Other palaeontologists, however, have pointed out that the overall similarities of both Chinji and Nagri faunas are with European faunas of later Miocene age⁵. Thus Pilgrim⁶ and others consider that the Dhok Pathan is equivalent to Pontian faunas from the so-called Pikermian in Spain and from the classic area of the *Hipparion* fauna, Pikermi in Greece; that the Nagri is equivalent to pre-Pikermian (in Spain, Vallesian) faunas; and that the Chinji is equivalent to pre-Pliocene faunas.

Vallesian and other pre-Pikermian faunas contain primitive *Hipparion* species, whereas species from "typical" Pontian deposits are more advanced. In Europe and Africa, *Hipparion* is unknown before the Vallesian (or Vallesian equivalent)^{7,8}. Clearly therefore the presence of *Hipparion* in the Chinji can be explained by one of the following alternatives only: (1) Chinji *Hipparion* species appear earlier in India than elsewhere; (2) *Hipparion* does not occur in the Chinji, and reports of its presence there are incorrect; in this case the Chinji is a Sarmatian equivalent.

Recently, Dehm⁵ has stated his belief in the second alternative, a view also favoured by two of us^{9,10}. Kurtén⁴, however, apparently unaware of Dehm's report, has continued to accept the existence of Chinji *Hipparion*.

More recently, Hussain has pointed out¹¹ that regardless of the validity of the occurrence of the *Hipparion* reputed to have been found near the base of the Chinji, the teeth of these specimens are very large. It is implausible that such animals should have preceded in time the smaller and structurally different species *Hipparion nagriensis* Hussain. We believe that these teeth are either not representative of *H. theobaldi* from the Dhok Pathan deposits or, if they are, they are not derived from Chinji levels. Accordingly, we have undertaken a re-examination of those specimens of *Hipparion* in North American collections which are reportedly from the Chinji zone. (It should be noted that most earlier workers in the Siwaliks relied heavily on the purchase of specimens from local collectors, a practice which generally makes accurate stratigraphic placement of specimens impossible and in turn prevents sound phylogenetic and ecologic interpretation.)

The first reason to suspect the validity of the occurrence of Chinji *Hipparion* is the small number of specimens known

to have been collected. Where *Hipparion* does occur it is typically found in large numbers, representing, for example, a fair percentage of the Nagri and Dhok Pathan faunas. Of sixty-two specimens of *H. theobaldi* in the American Museum of Natural History (AMNH) from Middle and Lower Siwaliks, only four are attributed to the Chinji. In the Yale Peabody Museum collections there are fifty *Hipparion* specimens from the Dhok Pathan, twenty-six from the Nagri and only two which are said to be from the Chinji. These two, recovered by De Terra's group (1935 field numbers 97 and 663), have now been transferred to the AMNH. Of the thirty-two specimens of *H. antilopinum* in the AMNH only one is attributed to the Chinji.

Another reason to be suspicious of the occurrence of *Hipparion* in the Chinji is that of the eight specimens supposedly from these beds, five of the six which can be identified to the species level are *H. theobaldi*. Two species of *Hipparion* occur in the Dhok Pathan, but in the Nagri only one, *H. antilopinum*, is found. If the Chinji specimens were truly from these beds, we would not expect them to resemble *H. theobaldi*.

Dehm⁵ collected in the Siwaliks in 1939 and again in 1955 to 1956. Not one specimen of *Hipparion* was discovered in the Chinji on either of his expeditions. He states that *Hipparion* was readily recovered in the Nagri but never in the Chinji, even in the richest localities. He collected more than 2,000 specimens from the Radipur area (Chinji) and from the composition of the fauna had no reason to suspect an ecological difference between this and Nagri localities which might account for the absence of *Hipparion*. Dehm⁵ cites examples of displaced specimens, demonstrating how other finds might have been falsely attributed to the Chinji.

The location and naming of the Chinji type area are confusing. Chinji village itself lies on Nagri age sandstone and the type localities for the formation lie within a belt of sandstone about 5 km wide to the south of the village. Dehm notes⁵ that in some of the Chinji outcrops, particularly to the south-west of the village, Pleistocene terraces with land and freshwater molluscs and ostracods occur suggesting that both Nagri and Dhok Pathan sediments might be washed onto the Chinji and not be recognized as younger sediments, particularly if collected by villagers. Human displacement and rediscovery are also possible in an area like this, for the children play with the fossil teeth as toys.

The following list presents the locality data on the eight specimens whose labels implied that they were from the Chinji zone. Colbert's maps¹ have been used to estimate placement of the localities. As will be seen, it seems that these finds were incorrectly labelled or were identified as to faunal zone without substantiation when they were catalogued.

(1) YPM 20063, *Hipparion*, molar secured by Lewis in 1932 but with questioned locality, "from Bhilomar?". Bhilomar is in the Nagri, near the Chinji-Nagri boundary.

(2) AMNH F. No. 663, *H. theobaldi*, right upper molar, collected by deTerra's expedition in 1935 labelled from the Chinji—"Chinji, Punjab", has a note with the specimen which says "locality unknown".

(3) AMNH F. No. 97, *Hipparion*?, tooth, collected from locality 68, Ramnagar, Kashmir. The exact correlation of the Kashmir sediments and faunas with those of the type areas of Chinji and Nagri in West Pakistan is uncertain.

(4) AMNH 19555, *H. cf. theobaldi*, tooth, collected by Brown in 1922 from "2 miles west of Chinji Bungalow". Two miles directly west of the bungalow is in the Kamliyal zone, very close to the lowermost Chinji, an improbable level in which to find a Dhok Pathan species.

(5) AMNH 19573, *H. theobaldi*, teeth, collected by Brown in 1922 from "Middle or lower Siwaliks". A note attached to this specimen states "Middle Siwaliks 3 miles northwest of Chinji—only one horse tooth so far in the Lower Siwaliks and I suspect it came from this Siwalik horizon". The meaning of this note is unclear. Three miles north-west of Chinji is definitely in the Nagri.

(6) AMNH 19584, *H. theobaldi*, five "miscellaneous teeth", acquired by Brown in 1922 from "5 miles east of Chinji Bungalow". This would place the locality in the Kamliyal.

(7) AMNH 19590, *H. theobaldi*, left upper molar, Brown 1922, from "1 mile north of Chinji Bungalow". Such a locality would be in the Chinji.

(8) AMNH 19661, *H. antelopinum*, teeth and jaw fragments, collected by Brown in 1922, from "Lower Siwaliks-quarry $\frac{1}{2}$ mile south of Dhok Pathan". This locality is in either the Dhok Pathan or Nagri zones.

If the locality data were accurate and reliable, the first appearance of *Hipparion* would have to be placed before Chinji time on the basis of one specimen, or possibly two. Its presence in the Chinji would be documented by, at most, three specimens; definite documentation, if the accompanying record is reliable, would be provided only by one specimen. It thus seems that a correlation based on the occurrence of *Hipparion* in the Chinji cannot be justified, and that Pilgrim's relative dating⁶ based on the remainder of the fauna is acceptable.

Should *Hipparion* have first appeared in the Siwaliks in beds of Nagri age as seems to be the case, then the Chinji deposits can be dated between about 12 and 15 million years; the youngest Nagri beds are probably 9 or 10 million years old. Thus *Dryopithecus* and *Ramapithecus* species from India and Pakistan span a period of some 4 to 6 million years. The oldest *Ramapithecus punjabicus* specimens from the Chinji horizons are therefore probably as old as the East African *Ramapithecus* from Fort Ternan in Kenya, dated radiometrically to around 14 million years².

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Syphilis and Neanderthal Man

BONE changes in Neanderthal remains which, it has been suggested¹, might be caused by rickets are not unlike those seen in certain treponemal diseases, notably congenital syphilis. Examining the Neanderthal collection at the British Museum (Natural History), I noted several features compatible with treponemal disease.

The Olympian brow, Parrot's nodes and Caput Quadratum are all examples of "bossing"² of the congenital phase of syphilis. These changes are well marked in the Gibraltar II and in the original Neanderthal skull and also appear in the descriptions of Staroselje³ and Pech de l'Aze⁴ remains. The thinning and pitting of the occipital and parietal areas with the relative depression of the bridge of the nose ("saddle nose") may support a diagnosis of a generalized syphilitic osteo-

myelitis. It is interesting that these changes persist into adult life. These changes were seen in both adult and child skulls.

The frequent lack of incisors and well worn flattened taurodont molars superficially suggest the crateriform decay of Moon's mulberry molars⁵, which are seen in congenital syphilis. Examination of the inner aspect of the calvarium shows no increase in vascular markings, making an external hydrocephalus unlikely. Some authorities have suggested, however, that there is evidence of a healed meningitis occurring⁶.

It was the inspection of the curves of the long bones, in particular, the backward curves of the femur and perhaps the changes at the metaphysis, that first made Virchow⁶ express his view that Neanderthal man was none other than *H. sapiens* with rickets. The effect of a syphilitic osteitis could produce these bone changes and might, in addition, account for the Neanderthal long bones being so short and stout⁷. Bowing of the tibiae¹ has also been described but was not present in the specimens I examined.

In societies with poor nutrition, rickets and congenital syphilis frequently occur together. The distinction between the two is extremely difficult without modern biochemical, serological and radiographic aids⁸. The degree of confusion can be gauged by Parrot's untrue aphorism "without hereditary syphilis, there is no rickets"⁹. If rickets were widespread in Neanderthal man, osteomalacia would occur in the adult female pelvis, making parturition exceptionally difficult. There was, however, no evidence of this in the Neanderthal and Tabun specimens, or in innominate bones examined by other workers¹⁰.

The oldest treponemal disease known at present is pinta (caused by the organism *Treponema carateum*) which dates back 15,000 years¹¹. The changes described in Neanderthal man may thus provide a possible link between the human and the yaws-like treponemal disease found in monkeys¹².

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Non-ferritin Iron Compound in Rat Small Intestinal Mucosa during Iron Absorption

THE transfer of iron across the mucosal cells of the small intestine is an active metabolic process, and part of the iron taken up by the cells is rapidly delivered to the plasma while some of the remaining iron is deposited as ferritin¹. A study of the subcellular distribution of orally administered ⁵⁹Fe in

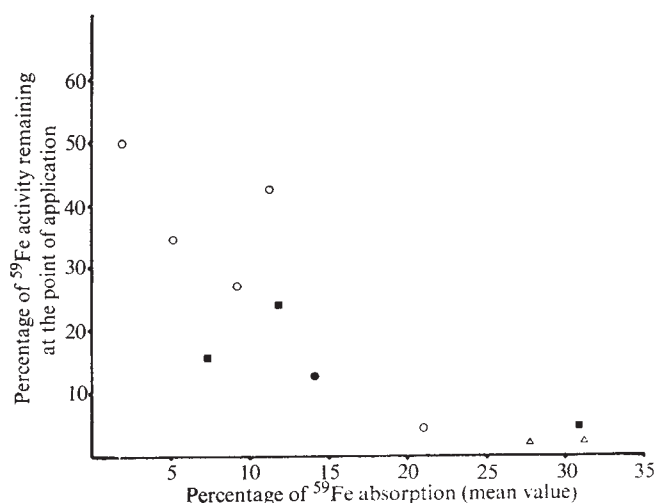


Fig. 1 ⁵⁹Fe activity remaining at the point of application after starch gel electrophoresis plotted against the mean absorption of the dose of ⁵⁹Fe by the groups of rats. The time intervals between administration of ⁵⁹Fe and removal of the intestine were: 15 min (●); 30 min (○); 1 h (■), and 4 h (△).

rat intestinal mucosa has shown that the greater part is present in the soluble, non-particulate fraction, although 12–18 h after the oral dose there is some concentration of ⁵⁹Fe in the mitochondria². We have studied the iron compounds present during absorption by electrophoresis of the soluble fraction of the mucosal homogenate.

Groups of four male Wistar rats, weighing about 250 g were given 5 μ Ci of ⁵⁹Fe through a stomach tube. The dose consisted of 5 μ g of iron as ferric chloride in 1 ml. of 0.05 M HCl. The initial whole body activity was measured by placing each animal in a counter containing a ring of eight matched Geiger-Müller tubes and the rats were killed at intervals from 15 min to 18 h after administration of ⁵⁹Fe. After removing the stomach and the intestine the activity in the carcass was measured in the Geiger ring counter. The mucosa was removed from the first 40 cm of the small intestine and homogenized. The final supernatant fraction (fraction VII) was prepared from the filtered homogenate by differential centrifugation², concentrated to about 2 ml. by vacuum ultrafiltration, and stored at -10° C.

Starch gel electrophoresis was carried out by the method of Smithies³ in Tris-HCl buffer, pH 8.6 ($\mu=0.025$) and the bridge buffer was of ionic strength 0.1. The mucosal supernatant samples were run in trays of 20 $\times$ 2 cm, beside a standard horse spleen ferritin solution (Koch-Light Laboratories) for 12 h at 220 V at 4 $^{\circ}$ C. The movement of the ferritin was followed by the colour of the protein and after electrophoresis the gel was cut into 0.25 cm sections. The activity of ⁵⁹Fe in each section was measured in a well-type sodium iodide scintillation counter with an automatic sample changer.

No ⁵⁹Fe was lost during ultrafiltration of the mucosal supernatant, indicating that no low molecular weight compounds of ⁵⁹Fe were present. Electrophoresis of the concentrated solutions from groups of animals killed up to 1 h after administration of ⁵⁹Fe revealed two principal bands of ⁵⁹Fe activity. One moved towards the anode with a slightly lower mobility than the horse spleen ferritin and the other was only slightly removed from the point of application.

After 4 h only the ⁵⁹Fe corresponding to the ferritin was present, and because as much as 88% of the ⁵⁹Fe of the supernatant could be precipitated by anti-horse spleen ferritin serum, this band probably represents ferritin-bound ⁵⁹Fe.

Fig. 1 shows the percentage of ⁵⁹Fe activity remaining near the point of application for electrophoresis plotted against the mean ⁵⁹Fe absorption for each group of rats. There is a significant correlation between these two parameters ($r = -0.83$, $P < 0.001$) but not between the percentage of ⁵⁹Fe near the

origin and the interval between administration of the dose and removal of the gut. During the first 4 h after oral administration the relation between absorption and time interval is variable and depends largely on gut motility.

Charlton *et al.*⁴ demonstrated that between 15 min and 4 h after ⁵⁹Fe was fed to rats the small intestinal mucosa contained increasing amounts of ⁵⁹Fe ferritin. Our results confirm this. Charlton *et al.* also noted a non-dialysable substance containing ⁵⁹Fe, which remained at the point of application during starch gel electrophoresis of mucosal extracts. A similar "mucosal iron-binding protein" was described by Pearson and Reich⁵ and Blanc and Isliker⁶. However, none of these people related the amount of ⁵⁹Fe bound to such a substance to the process of iron absorption.

Our results suggest that the uptake of ⁵⁹Fe by intestinal epithelial cells in the rat during the early phase of iron absorption is characterized by the appearance of a high molecular weight non-ferritin compound from the cells. We suggest that an intracellular protein carrier is involved in the transfer of iron across the intestinal cell during the rapid phase of absorption.

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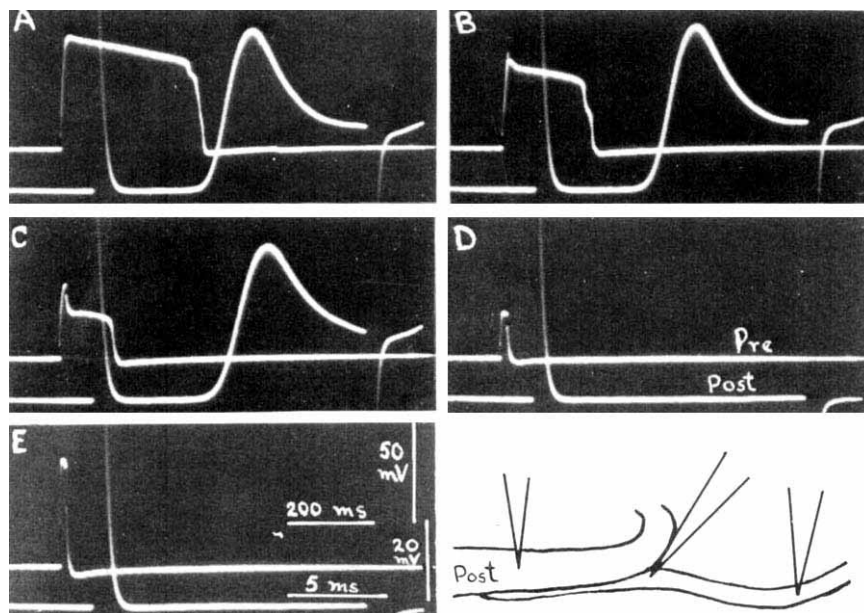
Lanthanum Ions abolish the "Calcium Response" of Nerve Terminals

It is well established that, in order to release transmitter, nerve impulses arriving at the terminals require the presence of calcium ions in the external medium¹. In the search for other ions which might replace calcium in the process of transmitter release at the neuromuscular junction, it has been found^{2,3} that lanthanum not only failed to substitute for calcium, but blocked transmission when added to a solution containing the normal amount of calcium. In these conditions, impulses still invade the nerve terminals but fail to release transmitter. It was thought that lanthanum might prevent calcium from crossing the nerve membrane and partaking in the subsequent reactions which lead to transmitter release.

It has recently been shown⁴ that after abolition of impulses by tetrodotoxin, the nerve terminals in the giant synapse of the squid can give a regenerative potential as a result of an inward movement of calcium ions. This required previous loading of the terminal with tetraethylammonium to reduce delayed rectification. The regenerative calcium response provides a suitable system for examining further the action of lanthanum on synapses.

I carried out experiments on the giant synapse in the stellate ganglion of the squid (*Loligo vulgaris*), using techniques previously described^{5,6}. Nerve impulses in pre- and post-synaptic axons were abolished with 10^{-7} (g/ml.) tetrodotoxin; and two intracellular electrodes were placed in the presynaptic

Fig. 1 Effect of lanthanum on the regenerative calcium response of the nerve terminal and the postsynaptic potential (upper and lower traces respectively) in the giant synapse of the squid. The two traces in each figure were obtained simultaneously but with different time bases as indicated in *E*, where the lower calibrations correspond to the records from the post-axon. *A*, 4 min; *B*, 21 min; *C*, 24 min and *D*, 34 min after starting perfusion with 4.5 mM lanthanum.



axon—one for recording the presynaptic membrane potential and the other for applying electric pulses to the axon. One of these electrodes was filled with tetraethylammonium and served also to inject this ion into the axon. A third micro-electrode was placed inside the postsynaptic axon to record synaptic potentials. In order to avoid precipitation of lanthanum, artificial seawater without NaHCO_3 was used for these experiments (mM: NaCl, 466; KCl, 10; MgCl_2 , 54; CaCl_2 , 11).

Fig. 1*A* shows the regenerative “calcium response” in a presynaptic axon of a ganglion in artificial seawater containing twice the normal concentration of calcium (that is, 22 mM), and 4 min after slow perfusion was started with a similar solution to which 4.5 mM LaCl_3 had been added. Fig. 1*B*, taken 21 min after introducing lanthanum, shows appreciable shortening of the regenerative response. With continued perfusion, the duration of the response further decreased and finally disappeared (Figs. 1*C* and *D*). Increasing the pulse strength in *E* did not restore the response. Fig. 1 also shows that the synaptic potential was abolished, which corresponds to the action of lanthanum at the neuromuscular junction^{2,3}, where lanthanum has been shown to interfere with the release of transmitter.

The experiments indicate that lanthanum (*a*) prevents the inward movement of calcium which is responsible for the tetrodotoxin-resistant regenerative response of nerve terminals; and (*b*) seems thereby to block synaptic transfer which depends on the inward movement of calcium that is required for normal transmitter release. These results may be interpreted in two ways depending on whether the site of action of lanthanum is assumed to be identical to, or different from, that of calcium. Thus lanthanum might compete with calcium for attachment to negative sites on the presynaptic nerve membrane. Alternatively, it could be that the binding of lanthanum to the membrane alters it chemically and changes its conformation in such a way that the calcium receptor sites are inactivated.

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Oral and Subcutaneous Administration of Monosodium Glutamate to Infant Rodents and Dogs

REPORTS by Olney¹ and Olney and Sharpe² implicate monosodium glutamate (MSG) as a specific central nervous system toxicant in infant animals. Within a few hours, subcutaneous and oral doses of between 0.5 and 5 g/kg body weight produced intracellular oedema and neuronal necrosis in the paramedian plane bordering on the roof and floor of the third ventricle. Preoptic and arcuate nuclei of the hypothalamus were reported to be selectively affected, as well as the scattered neurones within the median eminence (nuclei tuberales). In mice given similar doses of MSG in infancy and allowed to grow to maturity, excessive weight gains were reported after 60 days. The Olney studies and the inference of potential risk from the use of monosodium glutamate as a seasoning agent have been the subject of polemical communications^{3–5} and are under review by a committee of the National Academy of Sciences—National Research Council.

In comparative toxicological studies on rats (FDRL—Wistar derived), mice (C57Bl/6J), and beagles, we used appropriate controls with respect to both test materials and routes of administration. Except for the parent mice which were obtained from a commercial breeder, all animals were bred in the FDRL colony. Single doses were given either subcutaneously or orally at precise times after parturition to reproduce this phase of the Olney experiments. Solutions of MSG, monopotassium glutamate, sodium chloride, sodium gluconate, and distilled water were administered by both routes. Recognition was thus given to the role of both the sodium and glutamate moieties to the completely ionizable salt, sodium chloride, and to the less completely ionizable sodium gluconate. All doses were administered in 10% (w/v) aqueous solutions.

One series of mice and rats included 3 day old animals killed 24 h after single oral or subcutaneous doses administered between 1000 and 1200 h. Groups of five animals were used for each experimental treatment.

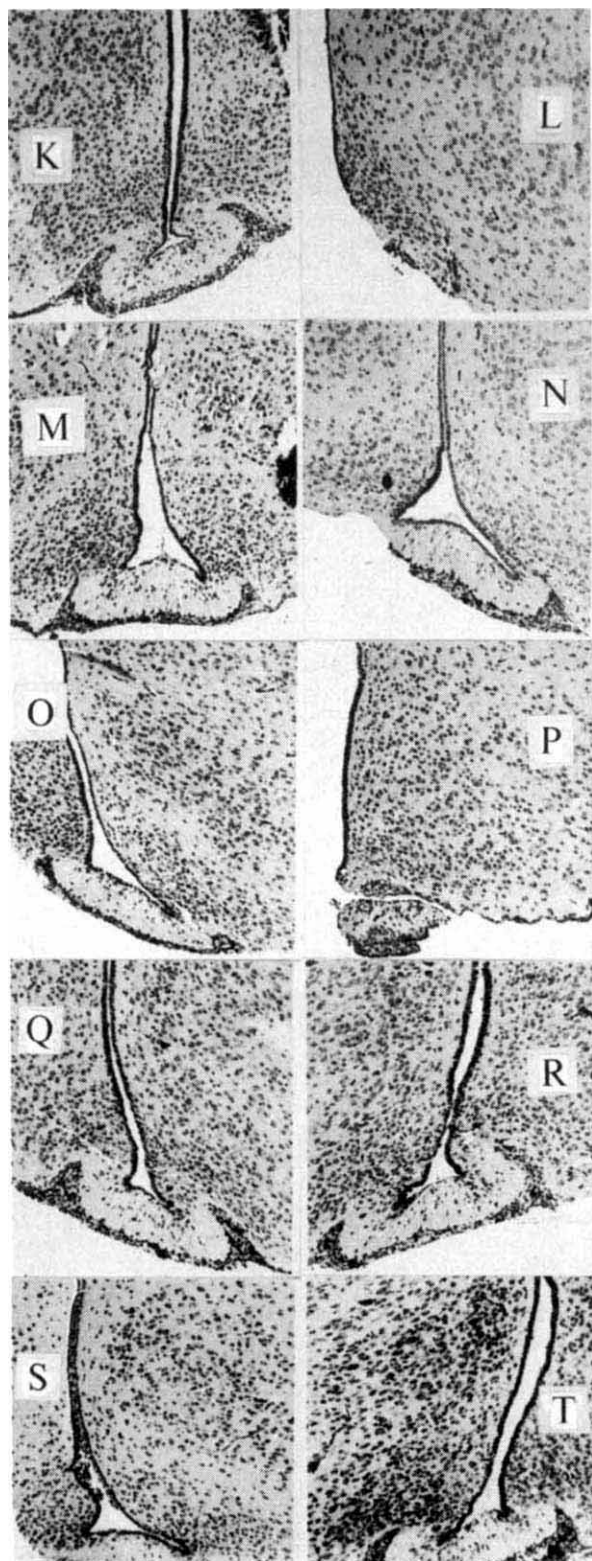


Fig. 1 Transverse ($\times 60$) sections, stained with haematoxylin and eosin through the hypothalamus at the level of the median eminence and arcuate nuclei. They represent 12 day old mice which received orally (left) or subcutaneously (right) monosodium glutamate (K and L), sodium chloride (M and N), sodium gluconate (O and P), monopotassium glutamate (Q and R) and water (S and T). These photomicrographs are characteristic of the findings in mice, rats and dogs at both levels (see text). The essential feature is the normal appearance and distribution of the neurones. T is an example of focal vacuolization of the ependymal cells, in 12 day old mice dosed subcutaneously with water. In K the arcuate nucleus has three small vacuolar spaces which, however, appear at higher power to be extracellular and may be artefacts. Similar changes can be found occasionally in almost all animals.

The age of the animals was taken into account inasmuch as MSG has been used as a food additive in baby foods. The period of introduction of "solid" foods into the diet of babies was reflected in a second series of rodents which were treated with a single dose at 12 days of age and autopsied 24 h later. At about 2 weeks of age, rats and mice begin to eat laboratory chow as well as taking maternal milk. The infant dog begins to ingest solid food after about 4 weeks and so for the beagles another series of experiments was started with single doses given at this time. The assignment of animals to treatment groups is shown in Table 1.

Mice and rats were autopsied after rapid anaesthetization with ether. Because neonatal and infant tissues are softer, it was possible to expose the brain, bisect it into right and left halves and remove it into fixative within 1–2 min. A further 1–2 min was needed to take multiple needle biopsies from the medial surface of the right half, through the areas of the pituitary base. These biopsy tissues and one eye were fixed in 3 per cent glutaraldehyde and subsequently stored in phosphate buffer at 4° C. The other eye was fixed in Zenker's fluid. The left half of the brain was fixed in 10% neutral buffered formalin, embedded in paraffin and 6 μ m sections were cut from the region of interest. Transverse (coronal) sections, which best exhibit the target site, were taken from all but a few of the animals. Between twenty and forty sections were examined from most animals.

For preservation, dog brain was perfused intravascularly with 3% glutaraldehyde for 5–20 min. Needle biopsies from half or, more recently, thin slices through the floor of the third ventricle were removed and, together with retina and nerve of one eye, were further fixed in glutaraldehyde and stored in phosphate buffer at 4° C. For light microscopy, the standard haematoxylin–eosin staining procedure was used. A minimum of ten sections per animal was examined. Where lesions were found, the glutaraldehyde-fixed tissues were examined by electron microscopy.

Examination of the 3 and 12 day old rats and mice and of the 3 and 35 day old dogs revealed no significant differences among the test and control groups with respect to any of the treatment variables—the test solutions, the routes of administration or the age of the animals when dosed or killed. The slides were read by two pathologists, one of whom read the slides blind, and who agreed in their observations and interpretations.

The tissue changes observed in most of the brain section consisted of occasional small neurones with pyknosis or large cytoplasmic vacuoles and a sparse scattering of cells, presumably macrophagic or inflammatory, typified by distinct eosinophilic cytoplasm and variable numbers of nuclear lobes or nuclear fragments of various sizes. They were more apparent in 3 day old animals in which neuronolysis and neuronophagia were also found occasionally. The incidence of these changes, however, was not related to treatment nor were they selectively localized. They seemed to be related to the rapidity of growth of the neonatal brain. Fig. 1 is representative of the observations in the oral and subcutaneous studies for each of the five dosing variables of the 12 day old young receiving the 1 g/kg dose of their respective test materials.

Monosodium glutamate, monopotassium glutamate, sodium chloride, and sodium gluconate at 1 g/kg in a 10% w/v solution (and comparable volumes of distilled water) were administered orally and subcutaneously to mice and rats at 3 or 12 days of age and to dogs at 3 or 35 days of age and the animals were killed within 24 h of dosage.

Examination of the eyes and of the preoptic and arcuate nuclei of the hypothalamus by two pathologists revealed no dose-related histomorphological effects in any of the test groups at either of the two ages selected to correspond to the periods before and at the beginning of solid food intake. We offer no explanation for the fact that the observations here reported do not confirm those of Olney and of Olney and

Table 1 Assignment of Animals to Treatment Groups

Material	Mode of administration *	Mice		Rats		Dogs			
		3 days	12 days 24 h	3 days	12 days 24 h	3 h	3 days 24 h	3 h	35 days 24 h
Monosodium glutamate	Oral	5	5	5	5	1	2	1	2
	Subcutaneous	5	5	5	5	1	2	1	2
Sodium chloride	Oral	5	5	5	5	1	2	1	2
	Subcutaneous	5	5	5	5	1	2	1	2
Sodium gluconate	Oral	5	5	5	5	1	2	1	2
	Subcutaneous	5	5	5	5	1	2	1	2
Potassium glutamate	Oral	5	5	5	5	1	2	1	2
	Subcutaneous	5	5	5	5	1	2	1	2
Water	Oral	5	5	5	5	1	2	1	2
	Subcutaneous	5	5	5	5	1	2	1	2

*Single doses of sterile 10% solutions of each (10 ml./kg body weight).

Sharpe after single doses of monosodium glutamate administered subcutaneously or orally to infant rats and mice.

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Possible New Metabolites mediating Actions of L-Dopa

It is generally assumed that the pharmacological actions of L-dopa (L-3,4-dihydroxyphenylalanine) are mediated through its conversion to dopamine. Thus, the specific value of L-dopa in the treatment of Parkinson's disease¹⁻⁴ would lie in its ability to traverse the blood-brain barrier and undergo decarboxylation in the parenchymal cells of the brain. It is likely that this mechanism operates physiologically in certain systems. But is dopamine the only metabolite mediating the action of L-dopa⁴⁻⁷? Some other simple derivative, formed in the brain by "conventional" pathways, may be pharmacologically active and responsible for the stimulation of dopamine-sensitive receptors that have been deprived of their normal presynaptic connexions through degenerative processes, as in Parkinson's disease, or by stereotactically placed lesions in experimental animals⁸⁻¹⁰. Another possibility lies in the conversion of L-dopa or one of its immediate products to some quite different compound, for example by condensation of dopamine with an aldehyde to form a tetrahydroisoquinoline. Reactions of this type are known for pyridoxal and its phosphate¹¹⁻¹³, as well as for 3,4-dihydroxyphenylacetaldehyde. The last compound arises from dopamine through the action of monoamine oxidase, and can condense non-enzymatically with dopamine to form tetrahydropapaveroline (nor-laudanosoline)¹⁴ as shown in Fig. 1. A Schiff's base is an intermediary in the reaction. Tetrahydropapaveroline possesses hypotensive

activity¹⁴. It is conceivable that a benzyl-tetrahydroisoquinoline, derived from L-dopa *in vivo*, has at least some of the pharmacological activities ascribed to this amino-acid in Parkinson's disease⁷. The type reaction described here has been demonstrated *in vivo*; in this case, 1-methyl-1,2,3,4-tetrahydroisoquinolines are formed^{15,16} by the condensation of catecholamines with acetaldehyde, the immediate dehydrogenation product of ethanol.

In the plant, compounds like tetrahydropapaveroline undergo phenolic oxidation, followed probably by a dienone-phenol type of rearrangement¹⁷, as proposed by Barton and Cohen¹⁸ in 1957. The products in this case are the positional isomers 1,2,9,10- and 1,2,10,11-tetrahydroxynoraporphine. The latter corresponds formally to 1,2-dihydroxynorapomorphine. An oxidation rearrangement of this kind occurring in the brain or other tissue would have considerable significance for future studies of the biochemical pharmacology of monoamines, for the formation of hitherto unsuspected types of metabolites would have to be reckoned with. Formation of a noraporphine derivative would bring the L-dopa treatment of Parkinson's disease a stage closer to recent pharmacological studies of the action of apomorphine. This alkaloid, like dopa¹⁹, stimulates the receptors of the trigger zone of the emetic centre, but the evidence is growing that this is but a model of the quite general stimulation of dopamine-sensitive receptors of the brain afforded by apomorphine²⁰⁻²³. A combination of enzymatic and spontaneous reactions, beginning with L-dopa and ultimately resulting in an apomorphine-like compound, might explain the persistent amelioration of symptoms of Parkinson's disease for some time after withdrawal of L-dopa therapy³. It is interesting in this connexion that apomorphine has a dopa-like action in Parkinson's disease^{24,25}, although the action is short-lasting. A noraporphine derivative formed *in situ* from repeatedly administered dopa might have a more enduring effect.

Finally, the resemblance of apomorphine and the tetrahydroxynoraporphines to bulbocapnine (Fig. 1), a potent catatonizing agent²⁶, is striking. Indeed, bulbocapnine may also act at dopamine-sensitive receptor surfaces in a sense opposite to that of dopamine and apomorphine^{27,28}, its catatonic effect then stemming from blockade of these post-synaptic receptors. It has already been shown that α -methyl-tyrosine, an inhibitor of catecholamine biosynthesis²⁹, produces a catatonic state in *Macaca mulatta* that is reversed by giving L-dopa³⁰. It seems clear that tests of aporphine derivatives in animals exhibiting dyskinesias as a result of specific brain lesions (ref. 31 and unpublished work of P. Bédard, L. Larochelle, L. J. Poirier and myself) would be valuable for the light they could throw on the role of dopaminergic fibres in the central regulation of motor activity. Such tests might even reveal "dopamine substitutes" with therapeutic value.

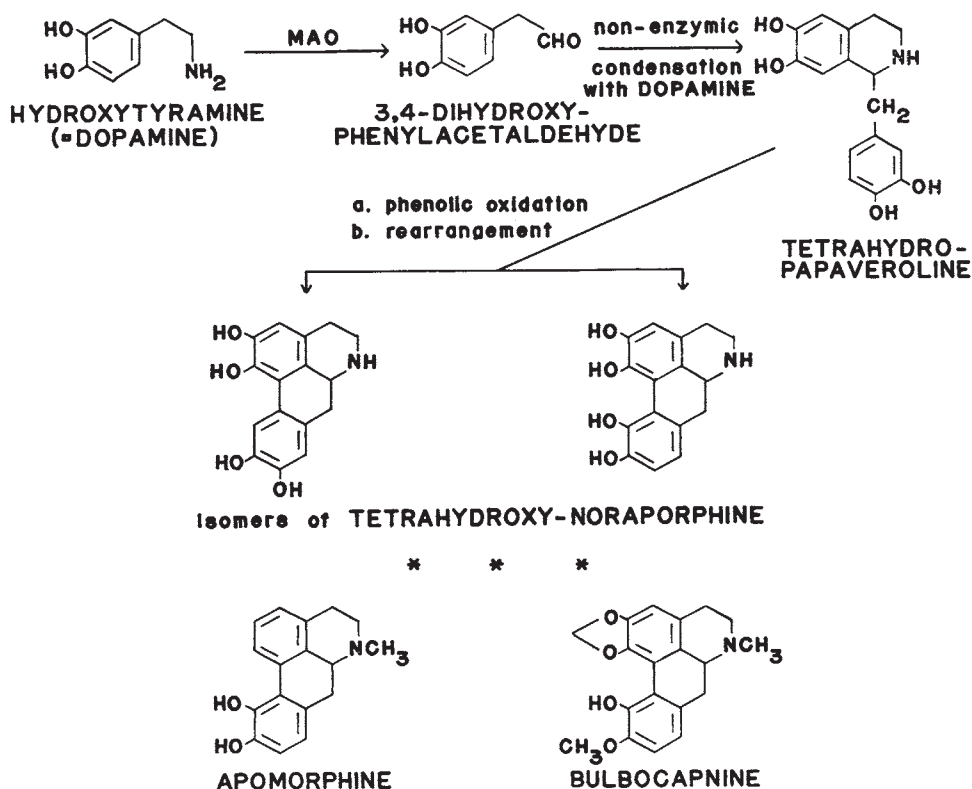


Fig. 1 Formation of tetrahydro-papaveroline, as demonstrated by Holtz *et al.*¹⁴, and its putative conversion to 1,2,9,10-tetrahydroxynoraporphine (on the left) and the 1,2,10,11-isomer. Structures of apomorphine and bulbocapnine shown at bottom for comparison.

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Therapeutic Implications in Parkinsonism of *m*-Tyramine Formation from L-Dopa in Man

THE urinary output of *m*-hydroxyphenylacetic acid is increased during treatment of Parkinsonian patients with L-dopa¹ and decreases significantly after administration of neomycin to reduce gut flora². Thus, it seems that *p*-dehydroxylation of this type is achieved by intestinal microorganisms³. Whereas earlier animal experiments had suggested that 3,4-dihydroxyphenylacetic acid is the immediate precursor of *m*-hydroxyphenylacetic acid⁴, we now have evidence of increased *m*-tyramine formation, indicating that some degree of microbial dehydroxylation of dopamine or of L-dopa itself takes place.

Urine samples (24 h) obtained from six patients with idiopathic Parkinsonism during a previous investigation² were stored at -15° C before assay. All patients were on their maximum tolerated oral dosage of L-dopa (Fig. 1). Collections had been made before taking neomycin and on day 3 of a short course of oral neomycin (1 g/day). Conjugates were hydrolysed by incubating 1% of the 24 h urine collection adjusted to pH 5.5, with 0.1 ml. of a sulphatase-glucuronidase preparation (suc d'Helix Pomatia, Industrie Biologique Français, Gennevilliers en Seine, France) at 37° C overnight. Amines were adsorbed on a column (1 cm bore) of cation exchange resin (AG 50W-X8, 3 g) and, after washing with 0.3 M sodium acetate (30 ml.), were

eluted with 30 ml. 3 N HCl in 50% ethanol. The eluate was evaporated under vacuum and the residue, containing phenolic amines, dissolved in 3 ml. of borate buffer, pH 10.3. The amines were then extracted with ethyl acetate (4 × 20 ml.) which was pooled and evaporated under vacuum. Half the residue was transferred quantitatively to a 10 inch square sheet of Whatman No. 52 paper for two dimensional chromatography in *n*-butanol-acetic acid-water (4 : 1 : 1) followed by anisole-acetic acid-water (50 : 50 : 9). Phenolic amines were located by spraying the chromatograms with diazotized sulphanilamide⁵. A yellow spot was detected which gave the same colour reaction with diazotized sulphanilamide as authentic *m*-tyramine and co-chromatographed with it in isopropanol-0.880 ammonia-water (8 : 1 : 1) and benzene-acetic acid-water (45 : 55 : 7), as well as the two solvents noted above. *m*-Tyramine was estimated visually by comparing the intensity of the unknown with spots obtained by subjecting suitable amounts of authentic *m*-tyramine (from Professor A. Pletscher, Hoffmann-La Roche, Basle) to the chromatographic procedure. When free amine was removed on resin before hydrolysis, it was shown that about half the total *m*-tyramine was excreted in conjugated form.

The daily excretion of total *m*-tyramine in five Parkinsonian patients before L-dopa therapy was about 50 µg/24 h and did not seem to differ from that of healthy adult controls. These values are of the same order as those reported by other authors in normal subjects⁶⁻⁸.

The ingestion of L-dopa resulted in a pronounced increase in *m*-tyramine excretion (Fig. 1) to a mean ± s.e. of 900 ± 200 µg/24 h. Output dropped significantly ($P < 0.001$) to 260 ± 110 µg/24 h after 3 days of treatment with neomycin. Thus neomycin-sensitive intestinal microorganisms play an important part in the formation of *m*-tyramine from L-dopa. The failure to return to normal excretion values is likely to be due to the relatively small dosage of antibiotic used.

m-Tyramine is probably formed from L-dopa by decarboxylation preceded or followed by *p*-dehydroxylation. It is not known which comes first: in certain circumstances, both transformations can be brought about by intestinal microorganisms^{9,10}, presumably in either order. The potential occurrence of increased amounts of the immediate product of L-dopa dehydroxylation, *m*-tyrosine, in Parkinsonian patients on L-dopa therapy, has some far reaching implications. Whether *m*-tyrosine is synthesized *in vivo* other than by bacterial action is as yet unknown. The profound pharmacological effects of administered *m*-tyrosine in animals^{11,12} presumably stem from its ability to cross the blood-brain barrier to be converted to *m*-tyramine: it is an excellent substrate for dopa decarboxylase¹³. One such action of *m*-tyrosine which may be of particular importance in the context of present day views of the biochemical basis of Parkinsonism¹⁴ is its ability to protect dopamine stores in the brain against depletion by reserpine^{15,16}. Reserpine, which is an effective depletor of cerebral monoamines, is sometimes responsible for a Parkinsonian syndrome in man¹⁷. Striatal dopamine concentration is also decreased in idiopathic Parkinsonism¹⁸. It seems just possible that the idiopathic disease derives from the toxic action of some unknown, perhaps endogenously formed reserpine-like substance. If this proves to be the case, then *m*-tyrosine may have a synergistic role in maintaining the concentrations of dopamine built up by L-dopa during treatment of Parkinsonism.

Although it has been tacitly assumed that the clinical improvement following L-dopa therapy in Parkinsonism stems from dopamine generation in the central nervous system, we have previously drawn attention^{1,2,14,19} to discrepancies between the timing of the clinical response, which is slow, and dopamine generation, which is rapid. We have therefore suggested, and others^{20,21} have concurred, that a study of minor metabolic pathways of L-dopa might be helpful. How then might *m*-tyrosine fit into this concept? Apart from its ability to protect monoamine stores from depletion^{15,16}, it possesses, in common with other potentially active metabolites synthesized by gut flora from inactive compounds²², one further

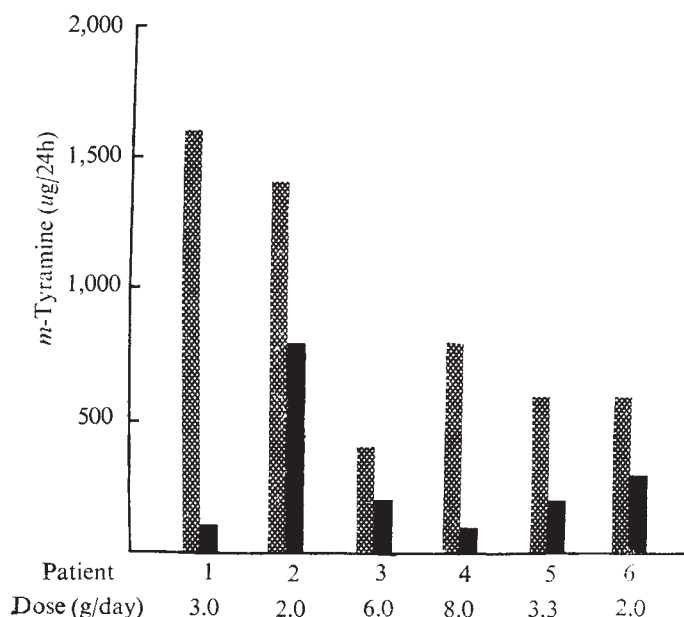


Fig. 1 Excretion of *m*-tyramine before (stippled columns) and during (black columns) day 3 of oral administration of neomycin (1 g/day). The subjects were six patients with Parkinsonism being treated orally with L-dopa in the doses shown.

characteristic: its production, to gauge from *m*-tyramine (Fig. 1) and *m*-hydroxyphenylacetic acid² generation, is likely to be extremely variable, corresponding with the presence of appropriate gut flora in a particular individual. If the bacterial production of cyclohexylamine from cyclamate²² can be quoted as a precedent, this ability may later be acquired during chronic consumption of L-dopa substrate, again with great individual variation. Translated into terms of clinical practice, the response to oral L-dopa in Parkinsonism varies considerably from patient to patient²³. Some patients may only obtain benefit after many weeks, while others may fail to respond altogether. While such unpredictability may derive from an inability to build up an effective local concentration of dopamine, for various possible reasons, it might equally well stem from a capricious production of *m*-tyrosine, sometimes insufficient to provide enough *m*-tyramine to maintain adequate striatal concentrations of dopamine.

If this hypothesis is correct, then (i) there should be a correlation between production of *m*-hydroxylated metabolites and clinical response to L-dopa in Parkinsonian patients; (ii) L-dopa therapy supplemented by oral *m*-tyrosine should achieve better clinical results than L-dopa alone. We are investigating both possibilities.

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DNA Repair Synthesis in Mammalian Cells exposed to a Series of Oncogenic and Non-Oncogenic Derivatives of 4-Nitroquinoline 1-Oxide

It has been repeatedly proposed that neoplastic cells arise from genetically heterogeneous populations. If so, carcinogens should induce genetically abnormal cells by increasing the frequency of mutations. The mutagenic capacity of carcinogens has been examined in *Drosophila*^{1,2}, *Neurospora*³, yeast⁴, transforming DNA⁵, and template activity of DNA⁶. Until recently, however, a study of chromatid aberrations and structural and numerical chromosome anomalies was the only way to examine the mutagenic effect of carcinogens on the tissues of complex organisms in which they induce neoplastic transformation^{7,8}. The disadvantage of this method lies in its restriction to numerical and structural chromosome alterations which represent only a part of the wide spectrum of all possible genetic changes elicited by a mutagen. In the work to be described here we have used unscheduled DNA synthesis as an indicator of DNA lesions⁹⁻¹¹. Derivatives of 4-nitroquinoline 1-oxide (4NQO) and related compounds were chosen because of their wide variance in oncogenic capacity¹²⁻¹⁵. Cultured Syrian hamster cells of the first to third passage were used. These cells are susceptible to neoplastic transformation *in vivo*¹²⁻²¹ and *in vitro*²²⁻²³ after exposure to the carcinogens used. Moreover, they respond to 4NQO induced DNA lesions with a readily analysed DNA repair synthesis²⁴.

The oncogenic 4NQO or one of its active metabolites seems to interact *in vivo* and *in vitro* with DNA causing single strand breaks^{6,25,26}. After the initial DNA damage there is a progressive increase in sedimentation rate²⁶ and unscheduled incorporation of ³H-thymidine²⁴. Our results are based on autoradiographic studies of the unscheduled incorporation of ³H-thymidine (Fig. 1).

The degree of repair synthesis in cultured hamster cells exposed to 4NQO and 4NPO derivatives and related compounds at concentrations ranging from 5×10^{-7} M to 5×10^{-5} M is shown in Table 1, with the relative oncogenic capacity of these compounds found *in vivo* by Nakahara *et al.*¹²⁻²¹.

Among the various isomeric nitroquinoline 1-oxides only the highly oncogenic 4NQO induced cell lesions resulting in an extensive DNA repair synthesis (first group in Table 1). On the other hand, virtually all substituted 4NQO derivatives examined elicited to various degrees a DNA repair synthesis (second group in Table 1). The data indicate a link between oncogenicity of a compound and its capacity to provoke DNA repair synthesis. Several simple patterns seem to emerge: only cells exposed to oncogenic compounds respond with DNA repair synthesis; the application of highly oncogenic derivatives initiates measurable repair synthesis at considerably lower doses than weakly oncogenic ones; and the maximum level of ³H-thymidine incorporation into cells exposed to weakly oncogenic derivatives is always lower than in tissues treated with highly oncogenic compounds. Among the quinoline 1-oxides grouped in the third paragraph of Table 1 the hydroxyamino derivative elicited DNA repair synthesis. It is also the only oncogenic derivative in this group, and is believed to represent the proximate oncogen¹². But 4NPO and the corresponding hydroxyamino derivative, 4HAPO, did not induce neoplasms or detectable DNA repair synthesis, although because this pair of pyridine derivatives is similar in structure and chemical reactivity to the corresponding quinoline derivatives, oncogenic activity has been expected in the past. The ability of pyridine derivatives to interfere with cellular DNA is, however, indicated by the relatively high DNA repair synthesis in cells exposed to 3-methyl 4-nitropyridine oxide.

The dose dependence of repair synthesis requires more detailed consideration. The highly oncogenic compounds in concentrations exceeding 10^{-5} M cause, with other phenomena, diminished repair synthesis. To find out whether the lack of detectable DNA repair synthesis in cells exposed to non-oncogenic 4NQO derivatives could be due to an inhibitory effect, cultured hamster cells were irradiated with a single dose of ultraviolet (900 ergs/mm²) and then exposed for 90 min to the non-oncogenic 8NQO and ³H-thymidine (Table 2). It seemed that 8NQO had no visible effect on repair synthesis in ultraviolet irradiated cells. Similarly, unscheduled DNA synthesis which followed an initial treatment with 4NQO (4×10^{-6} M for 90 min) was not significantly reduced by a subsequent application of 8NQO (1×10^{-4} M for 90 min). The absence of a DNA repair synthesis in cells exposed to non-oncogenic 4NQO derivatives cannot be traced to a toxic effect. The possibility that non-oncogenic derivatives can induce DNA lesions only at concentrations exceeding 1×10^{-5} M was examined by exposing cells for up to 6 h (ref. 3) to increased doses of 6×10^{-4} M. Unscheduled incorporation of ³H-thymidine was not observed.

Different oncogenic agents administered simultaneously, or the same carcinogens given in sequence, usually have a cumulative or at least an enhancing effect on tumour induction^{22,23}. Weak oncogenic activity is often only revealed when the agent is jointly applied with a carcinogen of known activity. This approach has identified 3-methyl-4NQO or 7-nitro-4NQO as weak oncogenic derivatives²⁴. This raises the question of whether an enhancing effect of two carcinogens is reflected in increased frequency of DNA lesions, leading to an increased repair synthesis. The weakly oncogenic 8-methyl-4NQO and 3-methyl-4NPO were added jointly to cultured hamster cells for 90 min and the DNA repair synthesis estimated. An additive effect is clearly shown by the data of Table 3. Similar enhancements of repair synthesis were obtained with several other combinations of weak carcinogens (for example, 3-methyl-4NQO and 4NQO) or with the joint application of a weak carcinogen and a strong carcinogen at a low concentration (3-methyl-4NQO and 2-methyl-4NQO). Increased unscheduled DNA synthesis, albeit not a strict summation, can also be observed in cells

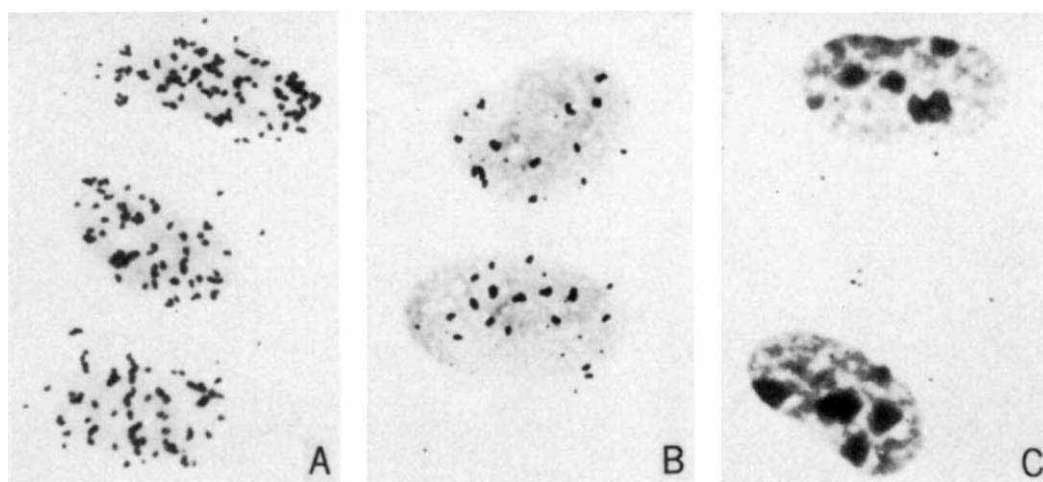


Fig. 1 Unscheduled incorporation of ^3H -thymidine into Syrian hamster cells exposed *in vitro* to the highly oncogenic 2-methyl-4NQO, (A); the weakly oncogenic 8-methyl-4NQO, (B); and the non-oncogenic 4-aminoquinoline (C); at a concentration of 1×10^{-5} M. To make sure that cells undergoing repair synthesis were not mistaken for those at early or late S phase or vice versa, we kept secondary cultures of Syrian hamster cells in arginine deficient medium (ADM) for 2–3 days before their exposure to the various 4NQO and 4NPO derivatives and ^3H -thymidine. Arginine deprivation seems to block the G1 to S phase conversion²⁷ without reducing the capacity of cells to enter repair synthesis²⁴. Indiscriminate averaging of autoradiographic grain counts from nuclei with 2C, 4C and 8C DNA might also have introduced errors. Grain counts were therefore restricted to small interphase nuclei which contained a 2C amount of DNA as estimated by microspectrophotometric measurements of the Feulgen reaction. A simple standardized procedure was adapted to compare repair synthesis in cultured cells exposed to strong, weak and non-oncogenic derivatives of 4NQO and 4NPO: seeding of 250,000 cells per cover slip (Leighton tubes), arginine deprivation for 2–3 days, exposure to various agents at concentrations ranging from 1×10^{-7} M to 5×10^{-5} M for 90 min, repeated rinsing in MEM without serum, submersion into 1% sodium citrate for 10 min, fixation in excessive amounts of alcohol-acetic acid (3:1) for 18 h with six changes of solution (4°C), air drying, staining in 2% orcein-acetic acid (50%), two changes in 20% alcohol (each 10 min), two changes in 10% alcohol (each 10 min), five changes in distilled water (each 10 min), air dried, dipped into Kodak NTB₃ emulsion, air dried for about 30 min, stored at 4°C for about 12–14 days, developed by the standard procedures, dehydrated and mounted in permount.

Table 1 DNA Repair Synthesis in Cells exposed to Various 4NQO Derivatives

Derivatives *	Oncogenicity†	Grains/nucleus concentrations					
		5×10^{-5} M	8×10^{-6} M	4×10^{-6} M	2×10^{-6} M	1×10^{-6} M	5×10^{-7} M
3NQO	— ¹²	0	0	0	0	0	0
4NQO	++ ¹²⁻¹⁴	14	101	66	51	43	19
5NQO	— ¹²	0	0	0	0	0	0
6NQO	— ¹²	0	0	0	0	0	0
7NQO	— ¹²	0	0	0	0	0	0
8NQO	— ¹²	0	0	0	0	0	0
2-methyl-4NQO	++ ¹³⁻¹⁴	59	88	63	36	25	10
3-methyl-4NQO	+ ¹⁵⁻¹⁶	7	2	1	0	0	0
5-methyl-4NQO	++ ¹²	15	44	21	12	7	3
6-methyl-4NQO	++ ¹²	14	63	39	29	15	7
7-methyl-4NQO	++ ¹²	41	57	57	41	9	9
8-methyl-4NQO	+ ¹²	21	5	0	0	0	0
6-n-butyl-4NQO	+ ¹⁵	13	52	20	4	0	0
6-t-butyl-4NQO	+ ¹²	32	14	4	0	0	0
6-n-hexyl-4NQO	+ ¹⁵	0	0	0	0	0	0
3-fluoro-4NQO	+ ¹⁵	3	4	1	3	0	0
6-chloro-4NQO	++ ¹²	10	42	51	38	26	12
6-carboxy-4NQO	+ ¹²	16	2	1	0	0	0
4HAQO	++ ^{18,19}	90	51	5	0	0	0
4-NH ₂ -QO	— ^{13,14}	0	0	0	0	0	0
4-OH ₂ -QO	— ^{13,14}	0	0	0	0	0	0
4-phenylsulphonyl-QO	— ²⁰	0	0	0	0	0	0
QO	— ¹³	0	0	0	0	0	0
4NQ	+ ²¹	28	9	4	0	0	0
4HAQ	?	0	0	0	0	0	0
4-NH ₂ -Q	— ^{13,14}	0	0	0	0	0	0
4NPO	— ^{13,14}	2	0	0	0	0	0
4HAPO	— ¹⁵	0	0	0	0	0	0
3-methyl-4NPO	?	30	1	0	0	0	0

* NQO: nitroquinoline 1-oxide; 4HAQO: 4-hydroxyaminoquinoline 1-oxide; QO: quinoline 1-oxide; 4NQ: 4-nitroquinoline; 4HAQ: 4-hydroxyaminoquinoline; 4NPO: 4-nitropyridine 1-oxide; 4HAPO: 4-hydroxyaminopyridine 1-oxide; Q: quinoline.

† ++: Strongly oncogenic. +: Weakly oncogenic. —: Tested but not proved to be oncogenic. ?: Not tested.

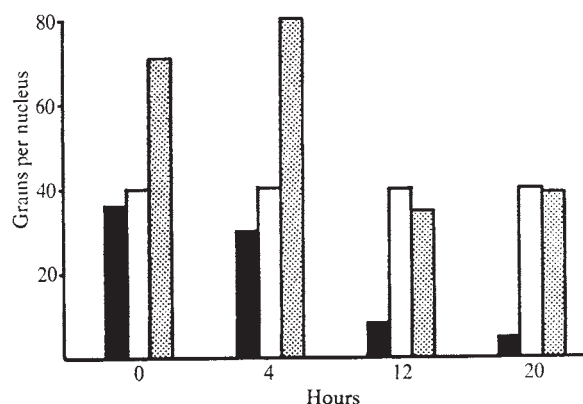


Fig. 2 DNA repair synthesis in Syrian hamster cells exposed to one dose of 4NQO (1×10^{-6} M) and a second one at various intervals. Black: first dose only; white: second dose only; dotted: first and second dose. Autoradiography.

irradiated with ultraviolet (single dose of 200 ergs/mm²) and exposed to 4NQO (1×10^{-6} M for 90 min).

The effect of spacing the application of two carcinogens was examined on hamster cells exposed to an initial dose of 4NQO and a second one administered at different time intervals. Repair synthesis was estimated after the second dose. An additive effect was found when the interlude did not exceed 10 h (Fig. 2). After this time a second treatment resulted in repair synthesis comparable with that caused by a single dose. The time when the effect of two doses of 4NQO ceases to be additive coincides with the reduction of DNA repair synthesis after ultraviolet irradiation or exposure to 4NQO¹⁸.

Table 2 Effect of 8NQO on DNA Repair Synthesis

	Grains/nucleus
8NQO (1×10^{-4} M)	0
UV (900 ergs/mm ²)	39.7
UV + 8NQO	34.5
4NQO (4×10^{-6} M)	44.2
4NQO + 8NQO	37.2

Table 3 Repair Synthesis in Hamster Cells exposed to Two Weak Oncogens

	0	8-methyl-4NQO 5×10^{-5} M
0	0 (0%)	24 (100%)
3-Methyl-4NPO 5×10^{-5} M	22 (100%)	57 (100%)

Cumulative effect: average number of grains per nuclei of cultured hamster exposed simultaneously to the weakly oncogenic 8-methyl-4NQO and 3-methyl-4NPO. Frequency of nuclei with repair synthesis is shown in parentheses.

Usually relatively large doses of 4NQO and its derivatives are used to measure DNA repair synthesis of single strand breaks with the caesium chloride technique. We therefore asked the following questions about the biological significance of such results. Is there any relationship between DNA damage induced and survival of cells? Are the doses of carcinogens necessary for a detectable reduction of molecular size or a measurable repair synthesis beyond a level tolerable by mammalian cells? We tried to answer the first question by exposing Syrian hamster cells to strong, weak, and non-oncogenic 4NQO derivatives and comparing their cloning efficiency (Table 4). The capacity of a compound to induce tumours, to elicit DNA lesions resulting in DNA repair synthesis, and to reduce the colony forming ability seem to be

related. An effect of various 4NQO and 4NPO derivatives on cell division was also revealed when the flow of cells into DNA replication at S phase was measured. This was done by arresting cells with arginine deficient medium, exposing them to various 4NQO derivatives, and triggering the initiation of S phase with arginine rich culture medium. The results show that only compounds active in eliciting DNA repair synthesis exert an inhibitory effect on the entry of cells into S phase. The same technique was used to answer our second question. We have previously shown the capacity of 4NQO treated cells to proceed to DNA synthesis at S phase before completion of their repair synthesis²⁴. This examination was extended to include the compounds listed in Table 1. Hamster cells exposed to a dilute concentration of highly oncogenic compounds or to larger doses of weak oncogens can enter and pass through a complete mitotic cycle in spite of repair synthesis already in progress. The criticism that DNA lesions resulting in measurable DNA repair synthesis can be only induced by lethal concentrations of a chemical agent seems unwarranted.

Table 4 Clone Forming Capacity

Derivatives	Oncogenicity *	Clones (%) at 2×10^{-6} M	5×10^{-7} M
3NQO	—	94	109
4NQO	++	0.5	3
6NQO	—	103	98
8NQO	—	100	103
2-methyl-4NQO	++	0.8	5
3-methyl-4NQO	+	57	75
6-methyl-4NQO	++	1	15
7-methyl-4NQO	++	0.6	7
8-methyl-4NQO	+	43	72
3-fluoro-4NQO	+	40	65
6-carboxy-4NQO	+	38	68
4HAQO	++	32	45
4-OH-QO	—	103	100
4NQ	+	75	87
4HAQ	?	101	96
4NPO	—	97	96
4HAPO	—	99	102
3-methyl-4NPO	?	33	43
Control (no derivative)		100	100

* See footnote Table 1.

In bacterial systems increased frequency of DNA lesions, reduced capacity for identifying and repairing these lesions, deficiencies in recombination, and the entry of unrepaired DNA into replication favour the occurrence of mutations^{30,31}. If a similar relationship exists in mammalian systems, then agents causing lesions in the DNA without impairing its replication should increase the mutation rate. At least two of the pre-requisites for mutations are met in 4NQO exposed hamster cells which are susceptible to transformation; first, DNA lesions occur, and second, the affected cells enter into DNA replication at S phase without completed repair synthesis. The difference between strong, weak and non-oncogenic derivatives of 4NQO or 4NPO derivatives could be deduced from their different capacities for inducing DNA lesions. Furthermore, one can assume that a prolonged and increased formation of mutant cells will lead to a heterogeneous cell population from which neoplastic cells can be selected. Whether this genetic concept of oncogenesis in its simplest form is applicable to 4NQO induced transformation is questionable. Another mechanism by which 4NQO may stimulate transformation was recently shown in our laboratory. Hamster cell cultures exposed to 4NQO before the addition of oncogenic SA7 virus show at least a twenty-fold increase in transformation frequency from cultures infected with SA7 alone. The enhancing effect is absent when comparable cell cultures are pretreated with a non-oncogenic derivative (6NQO). These observations suggest

an involvement of 4NQO induced DNA lesions in SA7 genome incorporation.

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IgG Subclass Specificity of Human Monocyte Receptor Sites

MONOCYTES as well as macrophages have receptor activity for IgG and the third component of complement¹⁻⁵. The receptor sites may act independently or cooperatively in binding and ingestion of red cell-antibody complexes²⁻⁵. Myeloma proteins of known subclass specificity used as inhibitors of phagocytosis of various red cell-IgG antibody complexes provided suggestive evidence for a subclass specificity of these receptor sites¹. We wish to report experiments which define this subclass specificity further and indicate similarities for the binding sites of both γG_1 and γG_3 .

Human monocytes were isolated from venous blood by a modification¹ of Bennett and Cohn's method⁶, allowed to adhere to a cover slip contained in Leighton tubes and washed free of both serum proteins and contaminating lymphocytes with Hanks solution. Various concentrations of purified⁷ and Gm-typed⁸ myeloma proteins were added to these mono-

layers. In control tubes human albumin, or Hanks solution free of proteins, was added to monocytes as indicated. Subsequently tanned⁹ human type O red cells coated with myeloma proteins or serum albumin (human or bovine) were added to give a final red cell concentration of 0.5%. The specificity of red cell coating was ascertained by haemagglutination tests with specific antisera. The ratio of red cells to monocytes was at least 50:1. After incubation of monocytes and red cells at 37° C for 60-90 min, the coverslips were removed, washed in Hanks solution, fixed in methanol and stained with May-Grünwald-Giemsa. The percentage of monocytes with ingested red cells was determined and the results were scored as described before¹.

In the first series of experiments aliquot red cells were coated with γG_1 by various concentrations applied (two-fold dilutions from 800 $\mu g/ml.$ to 6.3 $\mu g/ml.$). Significant phagocytosis by human monocytes was observed using red cells which were reacted with as little as 25 $\mu g/ml.$ of γG_1 . Higher concentrations resulted in up to 95% positive monocytes. The "average number" of γG_1 molecules per red cell sufficient for a positive reaction in this test system was estimated to be less than 700, but the significance of these calculations is restricted by as yet insufficient data on deviations around this mean and the possible occurrence of some red cells with a much heavier protein coat. Less than 5% of the monocytes ingested control red cells coated with human or bovine serum albumin and tested in parallel.

Red cells were then tested after application of myeloma proteins of the other γG subclasses; three different γG concentrations, 25 $\mu g/ml.$, 100 $\mu g/ml.$, and 200 $\mu g/ml.$, were evaluated. Red cells coated with γG_3 were positive in our test system, and phagocytosis by a significant percentage of monocytes was observed even when red cells had been coated with the lowest tested concentration of γG_3 . These results were comparable with those obtained with γG_1 . In contrast, within the range of γG concentrations evaluated, red cells coated with γG_2 or γG_4 were neither bound nor ingested by a significant number of monocytes.

Aliquots of tanned red cells were reacted with 200 $\mu g/ml.$ or 50 $\mu g/ml.$ of either γG_1 or γG_3 . The coated cells were extensively washed and then added to monocytes in the presence of various concentrations of isolated myeloma proteins; two different proteins of each subclass were tested. γG_1 in low concentrations inhibited binding and phagocytosis of red cells coated with either γG_1 or γG_3 (Table 1). Rosette formation and engulfment of both of these red cell preparations were also inhibited by γG_3 . Moreover, the amount of γG_1 or γG_3 in the incubation medium required for inhibition of either of these coated red cells was in the same range. When the heavier γG_1 or γG_3 coat was used, neither γG_2 nor γG_4 inhibited binding. When the lighter coat was used, a low degree of inhibition was observed with γG_2 or γG_4 , but with protein concentrations which were comparatively high (100 $\mu g/ml.$), which suggested that the result was related to contamination with normal γG_1 . As earlier experiments^{1,10} have shown, however, the test system was more sensitive when red cells were coated with small amounts of γG_1 .

Isolated human macrophages were a sensitive test system for investigating the interaction of red cell-bound immunoglobulins with mononuclear phagocytes^{1,3,4}. Only immunoglobulin molecules of the γG class attached to these cells, and reactivity was not confined to γG with anti-red cell antibody activity, but was also observed with γG bound to red cells non-immunologically^{1,4}. The minimal number of γG molecules bound by either mechanism and required for phagocytosis was of the same order (for comparison, see ref. 10). Extending earlier observations^{1,11}, this has shown that the receptor system for γG on monocytes interacted effectively with only the γG_1 and γG_3 subclasses. Inhibition experiments indicated that these subclass proteins interacted with the same receptor because both competitively inhibited binding of red cells coated with either subclass. As well as binding to mono-

cytes, these two subclasses also share the capacity of effectively reacting with the first component of complement¹². The binding site for complement has been defined to some extent¹³. Using a comparable test system in the guinea-pig, Berken and Benacerraf have shown³ that only γ_2 , which has the capacity to bind complement, but not γ_1 , attached to pulmonary and peripheral macrophages. In both systems a cooperative effect of the γG and C3 receptor has been documented^{2,5}. We have observed phagocytosis of red cells sensitized with rabbit γG anti-Forssman antibody. This reaction, too, was preferentially inhibited by γG_1 and γG_3 . Thus the cross-reactivity of γG_1 and γG_3 reported might indicate structural similarities involved in binding to monocytes, but further investigation is required to prove this possibility.

Table 1 Representative Experiment demonstrating the Specificity of the γG Receptor on Human Monocytes for γG_1 and γG_3

Red cell complex*	Inhibitor ($\mu g/ml$)	Phagocytosis by monocytes†
E-HSA	None	0
E- γG_1	None	++++
	HSA	++++
	γG_1 100	0
	10	0
	1	++
	0.1	++++
	γG_2 100	++++
	γG_3 100	0
	10	0
	1	++
	0.1	++++
	γG_4 100	++++
E- γG_2	None	0
E- γG_3	None	++++
	γG_1 100	0
	10	0
	1	++
	0.1	++++
	γG_2 100	0
	γG_3 100	0
	10	0
	1	++
	0.1	++++
	γG_4 100	++++
E- γG_4	None	0

* E-HSA, E- γG_1 and so on were tanned red cells coated with human serum albumin, γG_1 of a myeloma protein, or other immunoglobulins. A sample (200 $\mu g/ml$) of each protein was applied to a half volume of 33% red cells for coating.

† 0, Phagocytosis by up to 5% monocytes; +, phagocytosis by 6–25% monocytes; ++, phagocytosis by 26–50% monocytes; +++, phagocytosis by 51–75% monocytes; +++, phagocytosis by more than 75% monocytes.

If observations in this system can be extrapolated to conditions *in vivo*, findings that some antibodies contain only γG of certain subclasses¹⁴ gain further significance. The application of this test system for the investigation of red cell antibodies in terms of their interaction with isolated macrophages deserves further attention.

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Effect of Acetylcholine on Glycogen Formation and the Activity of Glycogen Synthetase in Isolated, Perfused Rat Liver

THE effect of adrenaline on carbohydrate metabolism in liver has been intensively investigated^{1–3}. On the other hand, very little is known about the role of acetylcholine⁴. The observation of Shimazu⁵ on the increase of the activity of liver glycogen synthetase after vagal stimulation induced us to investigate the possible effect of acetylcholine on carbohydrate metabolism in the isolated perfused rat liver. Part of the present results was reported elsewhere⁶.

Male Wistar Glaxo rats were used. They weighed from 200–250 g and were fasted about 48 h before use. Isolated rat liver was perfused by the procedure of Miller *et al.*⁷. Usually two parallel perfusions were run simultaneously; the perfusion medium consisted of washed erythrocytes and the constituents listed in Table 1. In a first series of experiments rat erythrocytes were used; in a second, beef erythrocytes.

Glucose and lactic acid were determined by enzymatic methods (Boehringer and Soehne, Mannheim); amino-nitrogen was estimated by the ninhydrin method⁸. Changes in liver glycogen content were estimated from the glycogen concentration in the caudate lobe removed at start of the experimental period and the final glycogen concentration, after 2 h of perfusion, in aliquots of the remainder of liver. In some experiments minor lobes were removed after 1 h. Glycogen was extracted by the boiling KOH procedure and estimated by the anthrone method⁹.

Glycogen synthetase activity was assayed as the rate of ¹⁴C glucose incorporated into glycogen, from ¹⁴C uridine diphosphoglucose, in the presence or absence of 10 mM glucose 6-phosphate^{10,11}. In the absence of glucose 6-phosphate the *a* form is measured; in its presence an inactive *b* form is activated and an estimate of total enzyme activity can be made¹¹. The active form of phosphorylase was measured in the direction of glycogen synthesis from glucose 1-phosphate, in the presence of 0.001 M adenosine monophosphate¹².

Before the response of the liver to acetylcholine was tested, experiments were conducted to determine the conditions which would stabilize liver glycogen during perfusion. The presence of an amino-acid mixture in a medium containing glucose about 10 mM was essential for the accumulation of glycogen⁶. In the absence of amino-acids, the isolated rat liver was able to increase the level of circulating glucose, whereas it was unable to accumulate glycogen to any significant extent, unless a high concentration of glucose was present in the perfusate. A similar finding had been obtained by Staib *et al.*¹³ working about the glucocorticoid control of carbohydrate metabolism.

When neostigmine (0.25 mg/h) was added to the perfusate containing amino-acids, and acetylcholine was infused at a constant rate (1 mg/h) the deposition of glycogen was increased and the output of glucose decreased (Table 1). The rate of gluconeogenesis, as calculated from the changes of perfusate glucose and liver glycogen, was not significantly modified.

Neostigmine alone was without effect. Cycloheximide reduced by about 70% the rate of gluconeogenesis, and prevented completely the accumulation of glycogen; the simultaneous treatment with acetylcholine restored gluconeogenesis to normal, but did not influence glycogen formation. This could indicate that the changes produced by acetylcholine on glycogenesis may require the synthesis of key enzyme(s). We feel, however, that in view of the rapidity of the response, further data would be required before this idea could be accepted.

The administration of carbamylcholine had essentially the same effect on the formation of glycogen as the treatment of acetylcholine + neostigmine, although it did not modify appreciably the output of glucose.

Neither acetylcholine nor carbamylcholine produced accumulation of glycogen in the absence of the amino-acid mixture (not shown) or in the presence of high concentrations of glucose (Table 1).

The concentration of lactic acid in the medium fell approximately at the same rate in control and carbamylcholine treated livers (Table 1); the ratio lactate used to glucose + glycogen formed, was respectively 2.14 and 2.06. Further, the level of amino-nitrogen in the perfusate diminished during the perfusions; in four experiments it was found that control livers took up in average 235 μg amine N/g/h, and the carbamylcholine treated livers 180 μg /g/h; the respective ranges were

Table 1 The Effect of Acetylcholine and Carbamylcholine on Glucose Output and on the Accumulation of Glycogen, in the Isolated Perfused Rat Liver

Exp. No.	Treatment	Change of perfusate glucose *	Change of liver glycogen † $\mu\text{mol/g liver}$	Change of carbohydrate in liver + perfusate	Change of lactic acid
Rat erythrocytes					
1	None	+93	+16.2	+109.2	
	Acetylcholine‡ + Neostigmine§	+21	+35.0	+56.0	
2	None	+40	+22.6	+62.6	
	Acetylcholine + Neostigmine	+24	+37.4	+61.4	
3	None	+12	+12.7	+24.7	
	Acetylcholine + Neostigmine	+10	+35.2	+45.2	
4	None	+52	+16.7	+68.7	
	Acetylcholine + Neostigmine	+30	+23.4	+53.4	
5	None	+101	+14.3	+115.3	
	Neostigmine	+82	+17.1	+99.1	
6	Neostigmine	+60	+6.0	+66.0	
	Same	+48	+7.0	+55.0	
7	Acetylcholine + Neostigmine	+30	+28.3	+58.3	
	Same + Cycloheximide	+72	+0.8	+72.8	
8	Cycloheximide	+18	-0.8	+17.2	
	Same + Acetylcholine + Neostigmine	+63	-0.6	+62.4	
9	Acetylcholine + Neostigmine	+36	+20.0	+56.0	
10	Glucose 24.4 mM	+6.2	+21.7	+27.9	
	Same + Acetylcholine + Neostigmine	-13.2	+24.4	+11.2	
11	Glucose 24.4 mM	-5.5	+18.0	+12.5	
	Same + Acetylcholine + Neostigmine	-13.0	+13.5	+0.5	
Beef erythrocytes					
12	None	+78	+10.1	+88.1	-150
	None	+58	+11.5	+69.5	-145
13	None	+79	+10.7	+89.7	-208
	Carbamylcholine¶	+97	+15.0	+112.0	-200
14	None	+92	+6.5	+98.5	-240
	Carbamylcholine	+53	+13.0	+66.3	-170
15	None	**	+10.1		-204
	Carbamylcholine	**	+21.8		-186
16	None	+58	+12.9	+70.9	-172
	Carbamylcholine	+37	+18.8	+55.8	-176
17	None	+78	+10.5	+88.5	-147
	Carbamylcholine	+93	+20.7	+113.7	-165

* With respect to the initial concentration (which was on average 10 ± 0.6 nm). † The initial glycogen level ranged from 1.5 to 3 $\mu\text{mol/g}$ liver wet weight. ‡ 1 mg/h, infused continuously. § 0.25 mg/h. || 3 $\mu\text{g}/\text{ml}$. of perfusate. ¶ 6 $\mu\text{g}/\text{ml}$. of perfusate. ** Not assayed.

The perfusate contained: 25 ml. of washed erythrocytes; 75 ml. of Krebs-Ringer bicarbonate solution; 2.25 g fraction V bovine albumin powder; 5,000 IU heparin; 150 mg glucose; 200 mg casein acid hydrolysate; 5 mg L-tyrosine and 5 mg L-tryptophan; 1 mmol of L-lactate was added at term of "equilibrium" period and 1 h thereafter. The perfusate was continuously gassed with a mixture of 95% O_2 and 5% CO_2 . The time of experiment was 2 h. All treatments were started at the end of "equilibrium" period. The blood flow varied from 15 to 18 ml./min and was not appreciably modified by acetylcholine. The production of bile was 0.3–0.4 ml./h. For other conditions see the text. The significance of the difference of each set of "treated" data with respect to "controls" has been calculated according to the *t* test and the following values were obtained. Glucose output: Controls or neostigmine 61 ± 10.5 ; neostigmine + acetylcholine 25.1 ± 3.7 ; $P < 0.05$ (controls 74 ± 5.45 ; carbamylcholine 70 ± 14.80 ; $P > 0.05$). Glycogen formation: controls or neostigmine 14.1 ± 1.9 ; neostigmine + acetylcholine 29.9 ± 2.9 ; $P < 0.01$ (controls 10.3 ± 0.73 ; carbamylcholine 17.8 ± 1.67 ; $P < 0.01$). Change of carbohydrate in the system: controls or neostigmine 75.1 ± 10.8 ; neostigmine + acetylcholine 55.1 ± 2.34 ; $P > 0.05$ (controls 84 ± 4.70 ; carbamylcholine 86 ± 16.25 ; $P > 0.05$). Uptake of lactic acid: controls 180 ± 14.1 ; carbamylcholine 179 ± 6.2 .

201–403 and 151–270 μg amine N/g/h. Thus it is not clear whether carbamylcholine reduced the uptake of amino-nitrogen.

The results we describe suggest that the most consistent effect of choline esters is enhanced deposition of glycogen. It is known that glycogen metabolism is controlled by two key enzymes, glycogen synthetase and phosphorylase. We were therefore interested in examining whether the induced alterations in rates of glycogen synthesis were paralleled by changes in activity of these enzymes. The experiments were conducted as follows: two minor lobes were removed just before connecting the isolated rat liver in the perfusion apparatus; the liver was then perfused in the presence or absence of carbamylcholine. Tissue samples were kept in liquid nitrogen until they were homogenized for enzyme assay. Perfusion of liver with the basic medium resulted in an increase of glycogen synthetase, α , which is presumably the only form active in the conditions existing *in vivo* (Table 2)¹⁴. Carbamylcholine produced a further increase of glycogen synthetase α . Total glycogen synthetase activity also rose, although less than the α form of the enzyme.

Table 2 The Effect of Carbamylcholine on Glycogen Synthetase Activity of Liver

No. expts.	Conditions	Activity of glycogen synthetase *	
		Form α	Total
5	Initial sample	10.1 $\pm$ 0.9	18.5 $\pm$ 1.1
5	Control perfusion †	15.3 $\pm$ 1.2	22.2 $\pm$ 1.4
5	Initial sample	9.6 $\pm$ 0.9	19.6 $\pm$ 1.5
5	Carbamylcholine ‡	19.1 $\pm$ 2.4	25.7 $\pm$ 1.7

Values represent means $\pm$ s.e. Liver donor rats were fasted 48 h. Tissue samples were homogenized with three volumes of cold 0.25 M sucrose, 0.005 M EDTA, pH 7.5, and centrifuged 10 min at 8,500g. Aliquots of the supernatant were incubated for 15 and 30 min for the determination of glycogen synthetase activity according to Villar-Palasi *et al.*¹⁰. For other experimental conditions, see text. The change of synthetase α activity produced by carbamylcholine is significantly higher ($P < 0.05$) than the change produced by infusion of the basic medium.

* μmol ¹⁴C-glucose incorporated into glycogen/g liver/h.

† Infused 20 min with the medium described in Table 1.

‡ Infused 20 min with the same medium, containing 5 $\mu\text{g}/\text{ml}$ carbamylcholine.

In the same conditions, glycogen phosphorylase was not modified by infusion of the medium alone (-6.5% ; range 0 to -19%), and was slightly decreased by treatment with carbamylcholine (-21% ; range -10 to -29%). It may be interesting to recall that De Wulf and Hers¹⁵ found that the administration of glucose or glucocorticoids *in vivo* to mice produces an enhancement of the activity of glycogen synthetase α , simultaneously with a small decrease of the activity of phosphorylase.

Two recent articles described an activation of glycogen synthetase α and an inhibition of phosphorylase in livers perfused with high concentrations of glucose^{11,14}. This may be the reason for the ineffectiveness of acetylcholine, when infused in a medium containing high glucose (Table 1).

Concluding, choline esters produced in the isolated, perfused rat liver an increased deposition of glycogen, which is paralleled by an enhanced activity of glycogen synthetase α and a small decrease of phosphorylase. The glucose output, although reduced by acetylcholine, seems to be not significantly altered by carbamylcholine. The rate of gluconeogenesis seems not to be significantly modified by either compound.

Further work is needed to clarify the physiological implications of these results. Probably, however, our data and the previous findings of Shimazu⁵ indicate a parasympathetic influence on liver carbohydrate. Shimazu and Amakawa provided a convincing demonstration that electrical stimulation

of sympathetic nerves causes a very rapid activation of liver phosphorylase and glucose-6-phosphatase^{16,17}. They suggested that this may be an emergency reaction of the animals to cause rapid glycogenolysis and glucose output, which may be then maintained and amplified by catecholamines. A similar situation probably exists for glycogen synthetase, which is increased *in vivo* by parasympathetic nerves and by insulin. Thus neural and hormonal mechanisms seem to be involved in the control of liver carbohydrate metabolism.

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Studies on the Antiviral Effect of Rifampicin in Volunteers

RIFAMPICIN¹ is a clinically useful, orally active antibiotic², synthesized from rifamycin SV (ref. 3), a product of *Streptomyces mediterraneus*. This antibiotic is effective in the treatment of a number of bacterial infections, especially in tuberculosis^{2,4}; it has also been shown to inhibit the replication of poxviruses in tissue cultures⁵⁻⁹. Further studies have indicated that the antiviral effect of rifampicin is selective in that it does not affect uptake into cells of some precursors, and also in that viruses other than poxviruses can replicate in the presence of the drug^{5,10}. The mechanism by which the selective antiviral effect is mediated seems to involve an inhibition of late viral protein synthesis¹¹, virion assembly¹² and possibly also the *de novo* synthesized viral polymerase¹³. More recent experiments (to be published) have shown that rifampicin inhibits the formation of lesions resulting from infection with vaccinia virus on the chorioallantoic membrane of embryonated

eggs, and on the skin of rabbits, when the drug is locally applied.

Both the *in vitro* and *in vivo* studies have suggested that rifampicin may have chemoprophylactic or therapeutic potential in human poxvirus infections. This has now led us to investigate the effect of rifampicin on the vaccination reaction in volunteers. These were medical students and staff 21–35 years old, who had previously been vaccinated but not within 3 years before this trial. They had no history of liver or kidney disease, no hypersensitivity to drugs or to egg protein, were free of generalized skin diseases and were not being treated with steroids at the time of the trial. Females were not included in the trial in which the drug was given *per os*.

Rifampicin was in one of two forms: either as capsules of 150 mg or 300 mg, or as a crystalline powder (working standard, lot 9024; microbiological potency = 984 µg/mg). This powder was used to prepare a 10% ointment (eye base ointment: 9 parts wool fat + 1 part yellow petrolatum) or a 15% cream (cold cream base: spermacetti, white bees wax, liquid paraffin, borax). The ointment and cream preparations, with or without rifampicin, were spread onto sterile gauze pads (5 × 5 cm) which were then applied to the vaccination site and closed with plastic, non-irritant, adhesive tape.

Vaccine was the DV strain of vaccinia virus grown on the chorioallantoic membrane (CAM) of 11–12 days old embryonated eggs. Vaccination was done by the multiple pressure method.

Local applications of rifampicin, both as a 10% ointment (trial 2), or as a 15% cream (trial 3), prevented the development of a positive vaccination reaction in approximately 50% of the treated arms, when compared with the control arms of the same individuals. These results demonstrated that rifampicin is capable of inhibiting the vaccination reaction in man when it is applied directly to the viral replication site.

The results of the serological tests are summarized in Table 2. Volunteers who were vaccinated on one arm (trial 1, control) had a mean HAI serum titre of 1/160 when tested 14–15 days post-vaccination. This represents an approximately 8-fold rise (seroconversion factor, SCF = 8) above the usual mean pre-vaccination titres which varied between 1/15 and 1/40. A similar SCF (=6) was found in the group which received virus on one arm and rifampicin orally (trial 1, treated). Antibacterial therapeutic doses of rifampicin did not therefore affect the normal immune response. Local application of a 10% rifampicin ointment (trial 2) to the vaccination site on one arm resulted in different SCF, depending on whether the vaccination reaction was positive or negative. Positive reactors, those in which the reaction developed in both treated and untreated arms, showed an SCF of 16. Negative reactors, those in which the rifampicin-treated arm showed no development of the vaccination reaction, had an SCF of 5. In the last group (trial 3), in which a 15% cream preparation of rifampicin was applied, the SCF was 2 in both positive and negative reactors. The neutralization

Table 1 Vaccination Reaction in Volunteers treated with Rifampicin

Trial	Route of drug administration	Group	Number of vaccinees	Cumulative number of positive reactors on day post-vaccination						Positive reactors (%)
				1	2	3	4	5	6	
1	<i>Per os</i> *	Control	10	0	0	7	10			100
		Rifampicin (12 mg/kg body weight)	8	0	0	3	6	7	8	
2	Local† (ointment)	Control (left arm)	9	0	0	7	8	9		100
		10% Rifampicin (right arm)	9	0	0	0	4	5		56
3	Local† (cream)	Control (left arm)	15	0	0	9	15			100
		15% Rifampicin (right arm)	15	0	0	4	6	7		47

* Subjects were vaccinated on left arm only, and the drug (12 mg per kg body weight, and not exceeding a total of 900 mg) was given once daily, starting 16 h post-vaccination and continued until typical reaction developed.

† In both these trials each subject was vaccinated in both left arm (control) and right arm (rifampicin treated). Drug was applied to vaccination site once daily, starting 16 h post-vaccination and stopped when typical reaction developed, or continued for a maximum of 10 days in negative reactors.

Blood samples were taken both pre-vaccination and 14–16 days post-vaccination (and in some cases also 3 months post-vaccination) and sera were tested for antivaccinia antibodies by (a) the haemagglutination-inhibition technique (HAI) using 8 HA units of vaccinia antigen prepared in CAM. Serum dilutions were made in 1% normal rabbit serum in saline. 0.25 ml. serum was mixed with 0.25 ml. antigen and incubated at 37° C for 1 h. One drop (0.05 ml.) of a 2.5% washed chicken red blood cell suspension was added and allowed to react at 37° C for 20 min to 30 min before reading the results. Titres of antivaccinia antibodies were defined as the first dilution of antiserum in which haemagglutination occurred. (b) The neutralizing technique using vaccinia virus strain WR, 150–500 plaque forming units and determining the effect on BSC-1 cells by the plaque method. Sera were heated at 56° C for 30 min, diluted in PBS and incubated for 30 min at room temperature with equal volumes of virus suspension.

Three trials were run and the results of these are shown in Table 1. When rifampicin, 12 mg per kg body weight², was given daily *per os* (trial 1), all subjects (8/8) showed a positive vaccination reaction. There was, however, a delay of 2 days, compared with controls, before 100% reactors appeared.

test supported these results. Because of this unexpected low SCF, sera were obtained again from this group 3 months later, tested and found to have a similarly low SCF. This finding eliminates the possibility of a delayed response in this group. The serologic analyses demonstrated a direct correlation between the vaccination reaction and seroconversion of HAI and neutralizing antibodies except in the group which was treated with the 15% rifampicin cream.

The results of this study show that the antibiotic rifampicin, which has previously been demonstrated to have an antiviral effect *in vitro*^{5,6}, can inhibit the vaccination reaction in volunteers. It is clear also from the results in volunteers that the vaccination reaction was dependent on the route of drug administration. When rifampicin was given *per os*, all subjects showed a positive vaccination reaction, indistinguishable from that in untreated control subjects. This dependence on route of administration is probably because local application results in higher concentrations of the drug at the site of viral replication. Where it has been measured², it has been found that rifampicin concentration in human skin after oral administration does not reach levels which are known to be effective against vaccinia virus *in vitro*^{5,6}.

Table 2 Seroconversion in Vaccinated Subjects

Trial	Route and dose of rifampicin	Vaccination reaction	HAI serum titre*		Seroconversion factor†	
			Prevaccination Range	Post-vaccination† Range	Mean	Mean
	Oral	Control (10)§	NA	—	1/40–1/320	1/160
1	(12 mg/kg body weight)	Positive				8
		Treated (8)	1/10–1/20	(1/15)	1/40–1/60	1/90
2	10% ointment	Positive (5)	1/10–1/40	1/20	1/40–1/640	1/320
		Negative¶ (4)	1/10–1/40	1/20	1/40–1/160	1/100
3	15% cream	Positive (7)	1/10–1/20	1/15	1/10–1/40	1/30
		Negative (8)	1/10–1/160	1/40	1/20–1/160	1/80

* HAI = First serum dilution giving a positive haemagglutination reaction.

† Taken 14–16 days post-vaccination.

‡ Fold increase in mean serum HAI titres pre and post-vaccination.

§ Number of cases.

|| NA = Not available.

¶ Negative reactors were those in which the reaction failed to develop in the rifampicin treated arm.

The finding that the vaccination reaction did develop in the rifampicin-treated arms of one half of the locally treated subjects requires explanation. This is unlikely to be because of a variation in individual response to the vaccine, for each subject served as his own control. It is possible that the virus inoculum and also the rate of viral replication varied in individual arms and might therefore have reached different levels at the time (16 h post-vaccination) rifampicin was applied. In this event the drug may have failed to inhibit the reaction in some cases but not in others. Further, because the actual amount of drug absorbed into the skin was not measured, differences in reaction could be accounted for by differences in effective drug concentration in individual cases.

The additional and unexpected finding in this study was the depression of the immune response to vaccinia virus. This phenomenon was not observed when the drug was given *per os* in therapeutic doses, nor when it was applied locally as a 10% ointment. It was only observed in that group of volunteers to whom the drug was administered as a 15% cream preparation. This suggests that the difference in effective concentration of rifampicin may be responsible for the immune depression. The fact that no increase in antivaccinia antibodies was found, though the vaccination reaction developed on one or even on both arms indicates the possibility that rifampicin affected local as well as distal immunocompetent cells. Further studies are required to establish this possibility. The question also arises whether or not the immune response is more sensitive than the viral response to rifampicin.

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Effect of Fluxes of Sugars and Mineral Ions on the Light Microscopic Structure of Frog Fast Muscle Fibres

THE transfer of skeletal muscle fibres from Ringer solution containing 100–200 mM glycerol, urea or other low molecular hydrophilic non-electrolytes to normal Ringer leads to the development of vacuolation clearly visible under the light microscope¹. In the case of glycerol efflux, vacuolation develops within a few minutes and persists for several hours, after which fibre structure is gradually restored to normal. Reimmersion of vacuolized fibres in glycerol-Ringer results in a rapid disappearance of vacuoles. The same effect is produced by the influx of some other low molecular non-electrolytes.

Electron microscopy^{2–5} shows that in the case of glycerol efflux the appearance of vacuoles is due to intense swelling of some portions of the transverse sarcotubules (T-system). This swelling is accompanied by the separation of the T-system tubules from the sarcolemma. As soon as vacuoles disappear, the T-system structure and its junctions with the surface membrane are restored to normal^{3,4}.

This communication gives a preliminary account of the alterations in muscle fibre structure revealed by phase-contrast microscopy during efflux of sugars and KCl and activation of the sodium pump⁶.

The work was performed in winter on small twitch muscle bundles (two to seven fibres) isolated from musculus ilio-fibularis of *Rana temporaria*.

The results of different experiments with sugar efflux are summarized in Table 1. Unless insulin is added to the incubation solution, the permeability of frog muscle to penetrating sugars (D-xylose, D-galactose) is very low⁷, and no vacuolation is obtained when it is returned to Ringer solution with or

Table 1 Effect of Sugar Efflux on Structure of Frog Muscle Fibres

Serial No.	Incubation solution	Time of incubation (min)	Washing out solution	Time of washout (min)	No. of fibres	% of vacuolized fibres during the first hour of washout	% of vacuolized fibres by the end of washout
1	R + 133 mM D-galactose	200	R + insulin	130	7	0	0
2	R + 133 mM D-xylose + insulin	1,300	„ „	220	24	100	72
3	„ „	220	„ „	220	32	100	81
4	„ „	70	„ „	150	20	100	100
5	„ „	240	„ + 1.5 mM phlorizin	170	31	52	0

without insulin. When 0.1 U/ml. of insulin was added both to the loading and to the washing out solutions, there was strong vacuolation during efflux of D-xylose and D-galactose. Morphological changes were similar to those observed with the efflux of glycerol and other low molecular non-electrolytes¹, the only difference being that with sugars there were no vacuoles near the surface of the fibre. The vacuolation during sugar efflux developed within 20–30 min and persisted in the majority of fibres for more than 3 h. Re-exposure of vacuolized fibres to sugar-Ringer (with insulin) led to disappearance of vacuoles within 20 min; glycerol-Ringer had this effect only when the vacuoles tended to disappear spontaneously. The presence of phlorizin, an inhibitor of sugar transport, in the washing out solution resulted in strong, although incomplete, repression of vacuolation.

Table 2 Effect of Different Substances on Structure of Vacuolized Frog Muscle Fibres

Serial No.	S	No. of fibres	After 30 min in R ± S		
			% of fibres with normal structure	% of fibres with partial normal structure	% of vacuolized fibres
1	+ 110 mM erythritol *	7	100	0	0
2	+ 220 mM D-xylose *	11	91	9	0
3	+ 110 mM D-galactose * – 55 mM NaCl	13	78	22	0
4	+ 220 mM D-galactose *	15	93	7	0
5	+ 220 mM D-galactose * + 1.5 mM phlorizin	14	7	21	72
6	+ 220 mM D-mannitol	13	0	23	77
7	+ 220 mM sucrose	20	0	30	70
8	+ 110 mM NaCl	17	0	6	94

Solutions: R + 220 mM glycerol → R → R ± S
Exposure: 80–150 min 30 min 30 min

* Penetrating substances.

Removal of vacuoles by sugars and related substances. Table 2 shows the effect of various sugars and polyhydric alcohols on fibres in which vacuolation had been induced by efflux of glycerol. Insulin was not added. Only penetrating substances (indicated by asterisks) were able to cause 80–100% disappearance of vacuoles within 30 min. This effect is less pronounced during spring and summer. Exposure of fibres with vacuoles

to solutions of non-penetrating sugars or to Ringer made hypertonic with NaCl led only to a partial normalization of structure in a small percentage of the fibres.

Because insulin was not present, only a very small quantity of even the penetrating sugars could enter the fibres during the 30 min of incubation⁷. But the experiments with phlorizin, which strongly inhibited the disappearance of vacuoles in galactose solution, indicate that the normalization of fibre structure was caused by slight penetration by the sugars. Thus the influx of sugars capable of causing vacuoles to disappear is much smaller than the sugar efflux required to cause development of vacuoles.

Another distinguishing feature of the fibre structure normalization under the influence of sugar influx is that in a great number of experiments, simultaneously with a complete disappearance of vacuoles inside the fibre, a number of comparatively large vacuoles appeared just on the fibre surface.

Vacuolation by efflux of KCl. The internal concentration of KCl in muscle fibres was increased by a 3 h exposure to Ringer solution plus 80 mM of extra KCl. During this procedure no morphological alteration of the fibres was noted. Fibres were transferred to different solutions with the composition shown in Table 3. The calculation showed that in all these solutions the driving force on K⁺ ions ($V_m - V_K$) was outward. As Table 3 shows, all fibres were vacuolated in all washing out solutions where $V_m - V_K$ was less than +50 mV. The first signs of morphological alteration of the fibres were registered in 5–15 min. Two or three hours later there was a complete or partial disappearance of vacuoles. The normalization of the structure proceeded much more rapidly if vacuolated fibres were transferred to Ringer solution with 220 mM glycerol or 80 mM KCl. The most intensive and persistent vacuolation occurred in the experimental series 3–5 (Table 3). In series 6, where the driving force on K⁺ ions was +50 mV, vacuolation was noted only for 30% of the fibres. At larger $V_m - V_K$ (series 7–10), vacuolation was observed in a few fibres and sometimes developed by the end of the experiment.

We think that the decrease or absence of vacuolation when the outward driving force on K⁺ ions is increased is connected with anomalous rectification of the muscle fibre membrane. According to Hodgkin and Horowitz⁸, there is a sharp decrease of potassium permeability when $V_m - V_K$ is in the range of +65 mV to +35 mV. Direct measurement of K⁺ fluxes has shown that the flux of K⁺ is greatest when $V_m - V_K = +10$ –+30 mV⁹, which agrees with our data (Table 3).

Vacuolation during stimulation of the sodium pump. A comparatively weak vacuolation which disappeared completely within 2–3 h was observed in 85% of cases ($n=77$) when fibres incubated for 40 h at 2° C in K⁺ free Ringer were transferred to Ringer in which 10 mM NaCl was replaced by 10 mM KCl. This procedure is known to activate the sodium pump^{10,11}. To check whether vacuolation is related to sodium pumping, we inhibited the sodium pump first by adding 10^{–5} M ouabain to the recovery solution ($n=33$), and

Table 3 Effect of KCl Efflux on Structure of Frog Muscle Fibres

Serial No.	Washing out solutions *					$V_m - V_K \dagger$ (mV)	Time of washout (min)	No. of fibres	% of fibres vacuolated during the first hour of washout	% of fibres vacuolated by the end of washout
	K ⁺ mg	Na ⁺ ion/l.	Cl ⁻	Sucrose mmole/l. l	Tonicity †					
1	62.7	133	197	0	1.0	+9	150	85	80	3
2	42.7	153	197	0	1.0	+19	180	58	100	4
3	32.7	163	197	0	1.0	+26	260	59	100	39
4	22.7	173	197	0	1.0	+35	320	75	97	40
5	12.7	113	127	0	0.65	+40	200	37	100	73
6	12.7	183	197	0	1.0	+50	290	80	31	15
7	12.7	113	127	140	1.0	+61	150	21	0	0
8	2.7	113	117	0	0.6	+75	290	61	0	16
9	2.7	193	197	0	1.0	+89	320	69	12	0
10	2.7	113	117	160	1.0	+105	170	16	0	0

* All the washing out solutions contain 1.8 mg ion/l. of Ca²⁺ and 2.3 mg ion/l. of HCO₃⁻. The composition of ordinary Ringer solution is shown in line 8.

† V_m and V_K were calculated by Nernst's equation for the first moments after the transfer of fibres to washing out solutions from a Ringer + 80 mM KCl. It was assumed that $V_m = V_{Cl}^8$, $[K^+]_i = 220$ mg ion/l., $[Cl^-]_i = 82$ mg ion/l. In series 5 and 8 corrections in intracellular concentration of K⁺ and Cl⁻ were made for changes of fibre volume.

† Relative to Ringer solution with added 80 mM KCl.

second, by maintaining the normal concentration of Na⁺ in this solution ($n=46$). In neither case was vacuolation observed in any fibre.

The ultrastructure of fibres that appear vacuolated by phase contrast microscopy is not known in all cases. But it is known that during glycerol efflux²⁻⁵, chloride withdrawal¹² or calcium withdrawal¹³, reversible vacuolation of frog muscle fibre results from the swelling of transverse sarcotubules. The same is true for crayfish, crab, and insect muscles during KCl efflux¹⁴⁻¹⁷. These data, as well as the similarity between changes in the light optical structure of fibres during the efflux of different substances, suggest that in my experiments, too, the T-system is responsible for vacuolation.

The mechanism of formation, and especially of disappearance, of vacuoles during efflux and influx of different substances is not clear. We suppose that these mechanisms must be similar to those involved in the swelling of lateral intracellular spaces, which is observed in different epithelia during activation of transport^{18,19}, that is, they are related to intracellular and intercellular flow of solutes and water.

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Inhibition of Macrophage Migration by a Soluble Factor from Lymphocytes stimulated with PHA or ALS

AFTER contact with an antigen *in vitro*, lymphocytes from guinea-pigs showing delayed hypersensitivity against this antigen release a soluble factor which interferes with the migration of normal guinea-pig macrophages from the capillary tube in which they are cultured (migration inhibitory factor, MIF)^{1,2}. This phenomenon has been considered as an *in vitro* model of delayed hypersensitivity³. Lymphocytes can also be stimulated by other factors such as phytohaemagglutinin (PHA) and antilymphocyte serum (ALS)^{6,7}. In addition to releasing MIF, sensitized lymphocytes cultured in the presence of the specific antigen undergo blast transformation, an increase in DNA synthesis and mitosis^{4,5}. It is not clear whether blast transformation and MIF releases are related phenomena⁸, but both may belong to the same sequence of cellular events, triggered by the binding of the "stimulating agent" to lymphocyte membranes.

We now report that, in the guinea-pig, contact of normal lymphocytes with PHA or ALS initiates the release of a factor which prevents migration of normal peritoneal exudate cells (PEC) from capillary tubes and which, following intradermal injection, elicits a skin lesion resembling a delayed hypersensitivity reaction.

Table 1 summarizes the methodological details and results of PEC migration in the presence of supernatants of cultures pulsed with ALS or PHA.

In eight out of nine experiments with ALS supernatants, PEC migration was inhibited; this inhibition, compared with the migration taking place in control supernatants, ranged from 18 to 54%. Migration in the presence of PHA supernatants was completely inhibited (Table 1). The possibility existed that this absence of migration resulted mainly from PEC death, for a strong cytotoxic effect of supernatants from PHA-pulsed

lymphocyte cultures has been described¹¹. As judged by the trypan blue exclusion method, however, the proportion of viable PEC after incubation for 24 h in PHA supernatants (44%) was similar to control preparations (50%).

Table 1 Inhibition of Macrophage Migration in the Presence of Supernatants from ALS or PHA-pulsed Cultures

Stimulating agent	Expt.	No. of capillary tubes	Inhibition (%) [*]
ALS	1	4	20
	2	4	43
	3	4	18
	4	6	54
	5	6	34
	6	4	48
	7	4	0
	8	8	29
	9	4	20
PHA	1	2	98
	2	8	95

^{*} Percentage inhibition =

$$1 - \left(\frac{\text{average area of migration in pulsed culture supernatant}}{\text{average area of migration in control culture supernatant}} \right) \times 100$$

Pulsed culture supernatants were prepared as follows. Suspensions of lymph node cells (10^7 cells/ml.) obtained from guinea-pigs injected with complete Freund's adjuvant were incubated at 37° C in 3 ml. cultures (10% de complemented normal rabbit serum in Eagle's) containing either ALS (12%, obtained as described by J. Foerster *et al.*⁹), PHA-P (1% of a stock solution rehydrated according to Difco Laboratories prescription) or no stimulating agent. After incubation for 2 h, the cells were spun down, washed three times in minimum essential medium and reincubated at 37° C in fresh medium. Preliminary observations showed that such "pulse exposure" to ALS or PHA, which we will refer to as "preincubation", was sufficient to induce a marked increase in DNA synthesis in subsequent stages of the cell culture. After incubation for 24 h the cells were spun down, the supernatants of triplicate cultures were pooled, and filtered through 'Millipore' filters 0.45 µm. Supernatants of cells "preincubated" in medium containing ALS, PHA or no stimulating agent will be respectively called ALS, PHA and control supernatants. These supernatants were used as culture media for capillary migration assays which were performed inside Mackness chambers as described by David *et al.*¹⁰, using guinea-pig PEC collected 72 h after intraperitoneal injection of 'Bayol F' mineral oil. Chambers were observed after 18, 24 and 36 h of incubation at 37° C. The area of migration in control culture supernatants (mean of four values) was usually slightly less than the area of migration in the presence of fresh medium.

The inhibition of migration could result from the liberation of MIF from lymph node cells after preincubation with ALS or PHA. It could also result from the release of ALS or PHA bound to the lymph node cell membrane because, when added to the medium of capillary tube cultures, these agents were found to induce inhibition of PEC migration; this inhibition was complete at high concentration, still observed at a final dilution of 1 : 6,000 for PHA and of 1 : 2,000 for ALS (Fig. 1) but was no longer detectable at greater dilution. These effects could be the result of a direct action on the migrating cells or to MIF release by the stimulated lymphocytes present in the PEC. Two types of experiment indicated, however, that MIF produced by the stimulated lymph node cells was the most likely mechanism for the inhibition observed with ALS or PHA supernatants.

First, these supernatants were assayed for the presence of small amounts of ALS or PHA. ALS was assayed by testing cytotoxic activity, using the dose response curve of C' dependent ⁵¹Cr-labelled guinea-pig lymphocyte lysis, as described previously⁹. Although unconcentrated ALS supernatant had no cytotoxic activity, a ten-fold concentration by pressure dialysis revealed a slight cytotoxic effect indicating that if ALS

were present in the unconcentrated supernatant, its concentration was lower than 1 : 3,000. When capillary tube assay was performed in the presence of a 1 : 3,000 dilution of ALS, migration was not inhibited, suggesting that the inhibitory effect of ALS supernatant was not a direct effect of residual ALS.

The presence of PHA in the PHA supernatants was assayed by determining the haemagglutinating activity (guinea-pig red blood cells) of these supernatants concentrated by lyophilization. This assay was considered valid because, although mitogenic and haemagglutinating activities seem to be functions of different subunits of the PHA molecule, they are both present in the intact molecule^{9,11}. No haemagglutinating activity was found in PHA supernatants concentrated ten times, while the assay is able to detect PHA at a concentration of 1 : 800, indicating that if there were any free PHA present in the PHA supernatant, it was at a concentration lower than 1 : 8,000. PHA added to the culture medium still had an effect when diluted 1 : 6,000 (Fig. 1) but had none at 1 : 12,000. This made it unlikely that the inhibitory effect of PHA supernatant was the result of free PHA.

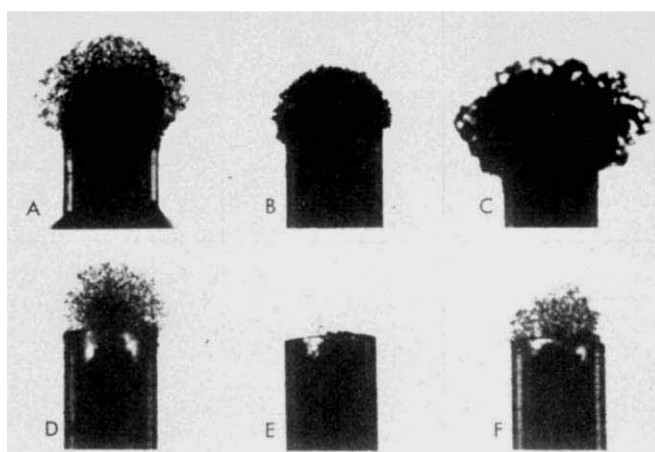


Fig. 1 Actual migration of normal peritoneal exudate cells cultured in: A and D, control supernatant; B, ALS supernatant; E, PHA supernatant; C, medium containing ALS 1 : 2,000; F, medium containing PHA 1 : 6,000. Expt. No. 2.

Second, in two additional experiments, puromycin (5 µg/ml.) was added to half of the cultures of lymph node cells pulsed with ALS and was subsequently removed from the supernatants by dialysis. These supernatants from ALS-pulsed cultures treated with puromycin failed to inhibit PEC migration, whereas those not treated with puromycin (but similarly dialysed) were inhibitory. These experiments suggested that the factor inhibiting capillary migration which is present in the culture fluid of cells stimulated with ALS requires, as does MIF, protein synthesis for its release¹³.

It has been proposed that MIF released by sensitized lymphocytes upon contact with the specific antigen plays a pathogenic role in delayed hypersensitivity, being responsible for the mononuclear cell infiltration characteristic of the lesions; indeed, intradermal injection into normal guinea-pig or an MIF-rich sample produces lesions resembling delayed hypersensitivity reactions¹⁴. If lymphocytes stimulated by ALS release MIF, one could expect injection of ALS supernatant or ALS itself to induce lesions of the delayed hypersensitivity type. Fig. 2 gives the details and histological findings of such an experiment in which ALS was injected intradermally into guinea-pig skin.

That the skin inflammatory reaction observed with ALS resulted, as in the *in vitro* assay, from the release of a factor from stimulated lymphocytes is suggested by this observation: one guinea-pig was injected as above with 0.1 ml. of ten-fold concentrations of several ALS supernatants or control super-

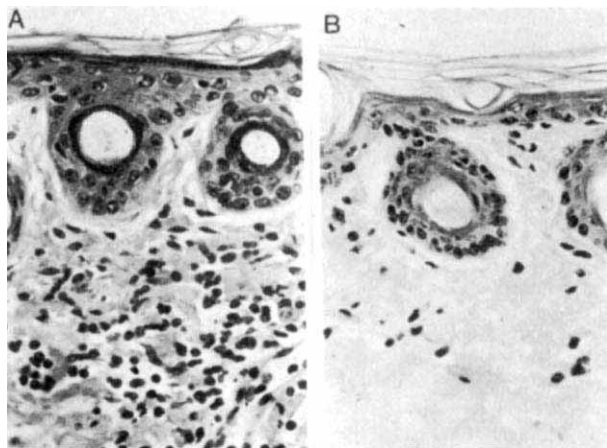


Fig. 2 Guinea-pig skin 16 h after injection with: A, 0.1 ml. ALS 1/10; B, 0.1 ml. of decomplexed normal rabbit serum (DNRS; 1:10). Two guinea-pigs were injected intradermally on one flank with 0.1 ml. of a 1:10 and a 1:100 dilution of ALS and on the other flank with the same dilutions of DNRS. After 16 h, the DNRS sites showed no macroscopic reaction while the ALS sites showed erythema and induration varying between 10 mm and 20 mm across. Histologically these ALS sites showed an infiltration of the dermis with mononuclear cells. ($\times 240$.)

natants from cultures set up in serum-free conditions¹⁴. After 8 h the ALS supernatant sites showed an erythematous and indurated reaction varying in diameter between 15 mm and 25 mm while the control supernatant sites showed only slight erythema without induration, averaging 3 mm across.

This observation is in agreement with the recent findings that both supernatants from lymphocyte cultures stimulated with specific antigen¹⁵ or plant mitogens¹⁶ contain skin inflammatory material. Our studies strongly suggest that a general consequence of lymphocyte stimulation, whatever the triggering mechanism, is the release of soluble factors which inhibit macrophage migration *in vitro*, produce mononuclear cell infiltration *in vivo* and possibly have the other properties of "lymphokines"¹⁵.

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Control of Bone Growth in Rats

THE longitudinal growth of bones is the result of cell proliferation within a comparatively simple linear system. When once the form of the epiphyseal growth plate has been established at about the time of weaning, the dividing cells arrange themselves in an orderly columnar pattern orientated in the direction of growth. Within each column there is a resting cell zone; a proliferation zone; a maturation zone where cells increase in size; and a hypertrophic zone in which the intercellular matrix becomes calcified before the cells are eventually invaded by metaphyseal capillary tufts.

The rate of bone growth is equal to the product of two factors, the rate of production of new cells per column and the average size of hypertrophic cells¹. We have measured the dimension of hypertrophic cells in the direction of growth and calculated it to have an average value of 30 μ m in 6 week old rats, 20 μ m in 16 week old rats and 25 μ m in young rats at 2 weeks after hypophysectomy. The principal influence on growth rate must therefore be the rate of cell production, which, in turn, could vary with changes in (a) the length of the proliferation zone, (b) the growth fraction, or (c) the average cycle time of proliferating cells.

We have accumulated data on the labelling index (percentage of nuclei labelled with tritiated thymidine 1 h after injection) and the size of the proliferation zone in cartilage plates which were under a variety of influences affecting bone growth. These data are presented in Fig. 1a and b as a series of labelling profiles for the proximal epiphyseal plate of the tibiae of rats. These profiles represent an analysis of the positions of labelled cells in the cartilage columns at 1 h after a tritiated thymidine injection. Because the number of cells per column varies by $\pm 25\%$, the positions have been adjusted by proportion to the average column length. The average number of hypertrophic cells per column is also shown. Cell No. 1 is taken at the epiphyseal end of the column and the limit of the count is the last cell not invaded by metaphyseal loops. The labelling profiles have been normalized to 100 cells and represent analysis of a total of 75–100 cells sampled from at least two rats. The labelling indices are given although it is necessary to know the duration of S phase to calculate the rate of cell production.

The two figures show that over a wide range of treatments which disturb the growth of bone, there is little change in the size of the proliferation zone except during chronic irradiation and in old age. This invariance in the length of the proliferation zone relative to the overall column length is particularly noticeable in rickets and following ³²P injection. Alterations in growth rate, therefore, must arise either from changes in the growth fraction or from the average cell cycle time. The growth fraction in young rats estimated by the semi-continuous labelling method seems to be nearly 100% (ref. 2), but there is evidence³ that this may be reduced in older rats. Irradiation probably lowers the growth fraction by inactivating cells in the proliferation zone.

The second observation to be made is that the general shape of the profiles does not change. The frequency of occurrence of labelled cells is lower in the top few positions (the resting zone). This is particularly significant when untreated hypophysectomized rats are compared with those which have been given growth hormone. The effect of growth hormone is on both proliferation and resting zones and not preferentially on the resting zone cells. Contradictory results have, however, been reported in rabbits⁴.

Two main controls seem to be acting on the growth plate; first, rate controls that affect the rate of division of the cells in the resting and proliferation zones; second, spatial controls acting to limit the size of the proliferative zone. A few of the factors that may affect the rate of division, even if indirectly, are listed in Fig. 1a. More complete surveys are given elsewhere^{5,6}. Vitamin deficiencies and conditions (including temperature⁷) that affect general metabolism may change the division rate of growth cartilage, but there are also specific hormonal controls. In most instances there is a chain of inter-

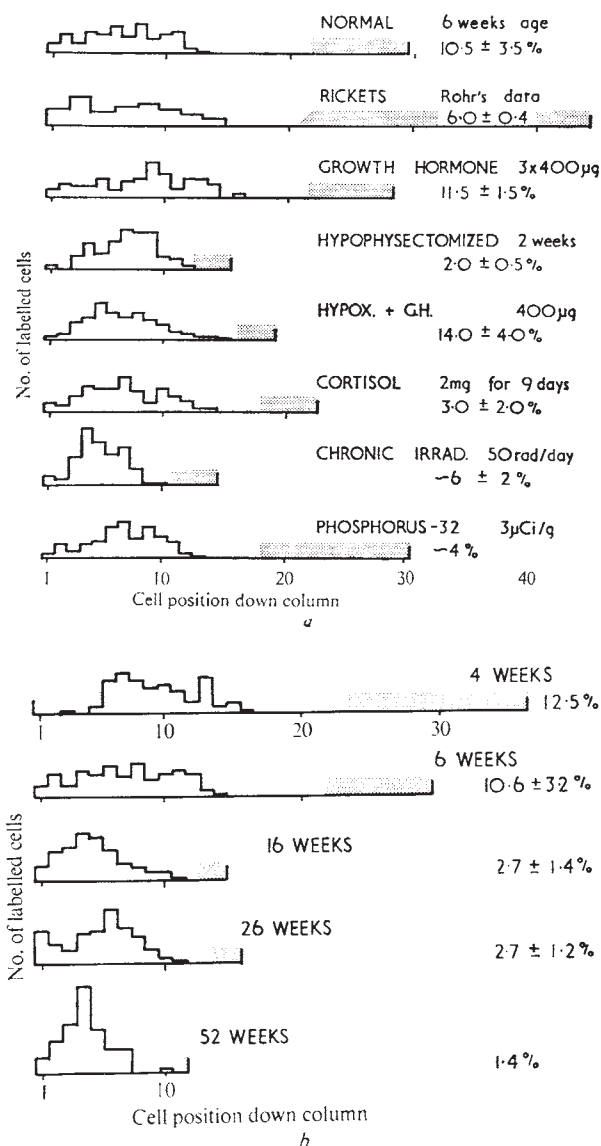


Fig. 1 (a) Labelling profiles of the proximal growth plate of the rat tibia. The shaded areas show the approximate lengths of the hypertrophic zones. Figures to the right of the profiles give the labelling index with standard deviation. Normal, 6 week old male Wistar rats; Rickets, weanling Wistar rats after 2 weeks rachitic diet (data from ref. 13); growth hormone: three daily injections of 400 µg (1 mg = 1 IU) of bovine growth hormone in 6 week old male Wistar rats; hypophysectomized, male Wistar rats hypophysectomized when 6 weeks old, data for 2 weeks after operation; hypox. + G.H., rats 2 weeks after hypophysectomy killed 24 h after receiving 400 µg of growth hormone; cortisol, 6 week old male Wistar rats given 2 mg daily injection of cortisol for 9 days; Chronic irradiation, 7 week old female August-Marshall F1 hybrid rats subjected to chronic gamma irradiation at 50 rads/day for 35 days; phosphorus-32, 7 week female August-Marshall F1 hybrid rats injected with 3 µCi/g ^{32}P , killed 4 weeks later. (b) Labelling profiles for male Wistar rats 4 weeks to 1 yr old.

actions linking cause with effect; for example it is known that the effect of growth hormone is mediated by sulphation factor⁸, but there is evidence from transplant studies^{7,9} that the basic growth controls are internal to the growth plate. There is less evidence on the control that limits the length of the proliferation zone. If differentiation from proliferation to maturation is triggered at a certain level in a diffusion gradient, then a constant length of zone would be expected but the available data on the direction of diffusion within growth cartilage are conflicting^{10,11}. A further possibility of controlling the number of cells per column in the proliferation zone is by setting a limit to the number of divisions that each

daughter cell of a resting cell may make. We tested this type of control on a computer model¹² and found it to be very insensitive.

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Impairment of Antibody Response and Recovery in Malarial Rodents by Antilymphocyte Serum

HETEROLOGOUS antilymphocyte serum (ALS) is a very potent inhibitor of cell-mediated immune responses such as homograft rejection and delayed hypersensitivity¹. It has also been shown to suppress the antibody response to inert antigens such as sheep red blood cells and bacterial products in rodents and other laboratory animals¹⁻³. By contrast, in the several infections of rodents in which the antibody response has been followed, including trichinosis in rats⁴ and several viral infections of mice^{5,6}, ALS impaired recovery, but the antibody response was not altered. It is therefore of interest that we have found a marked delay in the antibody response associated with delayed recovery from a malaria infection in ALS-treated mice.

NIH general purpose female mice were infected with the 17-X strain of *Plasmodium berghei*⁷. This strain causes a self-limited infection in mice and is therefore suitable for the study of the immune response. ALS was prepared in rabbits by the method of Levey and Medawar, using thymocytes from newborn mice⁸. Mice to be infected were divided into three groups containing ten mice each: an ALS-treated group, a control group treated with normal rabbit serum (NRS), and a control group receiving no treatment. Treated mice received 0.3 ml. of ALS or NRS intraperitoneally every three days, beginning three days before infection and continuing throughout the course of the infection. Parasitaemia levels were determined daily and fluorescent antibody levels were determined weekly on all mice by the method of Kuvn and Tobie⁹.

Fig. 1 shows the course of the parasitaemia and the specific antibody response for each group of mice. Mice in the control groups attained peak parasitaemia values of 20-30% and showed a rapid decrease of parasitaemias during the third week. By contrast, ALS-treated mice attained peak parasitaemia values of 70% and clearance of parasites was delayed

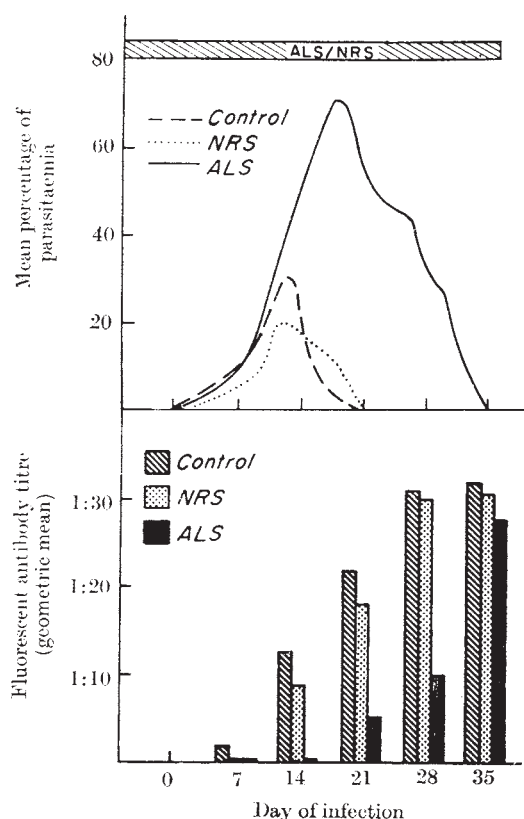


Fig. 1 Daily group parasitaemia levels (top); weekly fluorescent antibody titres (bottom).

until the fifth week of infection. By day 14, the untreated control and the NRS-treated mice showed significant increases in antibody titre, and peak titres were attained by day 28. At day 14, the ALS-treated mice showed no increase in titre. By day 21 they showed modest increases, and not until day 35 had they attained titres comparable to the other two groups.

This study shows that, in mice, ALS can suppress the antibody response to a replicating agent just as it suppresses the response to non-replicating antigens such as sheep red cells. As already noted, ALS treatment did not alter the humoral response of rodents to several other infectious agents. On the other hand, Wenner *et al.* have recently reported a delay in the antibody response to a monkey pox infection in ALS-treated cynomolgous monkeys¹⁰, a result similar to our own in mice with a malaria infection. It is reasonable to suppose that ALS may act similarly in man and that the suppression of the humoral immune response by ALS might interfere with the diagnosis of or recovery from some infections.

It is apparent from the appearance of antibody and recovery from the *P. berghei* infection that the effects of ALS were transient. This was probably because of the formation of antibody to the ALS, known to occur in rodents receiving frequent ALS injections^{2,11}.

The close temporal relationship of antibody synthesis and decrease in parasitaemia in all three groups of mice suggests that antibody participates in the recovery process. This possibility is supported by previous studies which showed that malarial antibody can passively protect infected humans and rodents¹²⁻¹⁴, and impair the *in vitro* proliferation of plasmodia¹⁵.

There is evidence from studies using neonatal thymectomy and passive transfer of lymphocytes that cell-mediated immunity may also participate in recovery from *P. berghei*¹⁶⁻¹⁸. Phagocytic activity by the reticuloendothelial system is essential to recovery¹⁹, and recently it has been suggested that interferon may be involved²⁰. In addition to antibody synthesis, each of these defence mechanisms may be impaired by

ALS^{21,22}, making it difficult to delineate the critical factors in recovery from infection by the use of ALS.

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Xg Blood Groups of Thais

SAMPLES of blood from 181 normal unrelated Thais from Bangkok have been tested for the X-linked blood group antigen Xg^a. The results are shown in Table 1.

Table 1 Frequency of Xg^a in Thais

	Xg (a +)	Xg (a -)	Total
Male	73	48	121
Female	46	14	60

The number is small but the results are sufficient to show that antigen is less common in Thais than in Europeans¹ and Indians², but more common than in Chinese³. Thai gene frequencies calculated from the male and female results are: Xg^a 0.57 and Xg^a 0.43.

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BOOK REVIEWS

Investment in Prestige

Dollars for Research. Science and its Patrons in Nineteenth-Century America. By Howard S. Miller. Pp. xi+258. (University of Washington: Seattle and London, 1970.) \$9.50; 90s.

DR MILLER'S book tells us how, in nineteenth century America, the advancement of basic research was often dependent on private philanthropy. Read in conjunction with Hunter Dupree's work on *Science in the Federal Government*, it helps to clarify certain long term trends in the history of American science.

Before exploring this theme, however, let me make one confession. The more I read of *Dollars for Research*, the more my interest (and even sympathy) began to shift from those who were receiving the money to those who were giving it. Three or four cases aside, the patrons portrayed here comprise a most extraordinary rogues' gallery of cunning, slightly alienated entrepreneurs. Not a few of them appear to have felt somewhat guilty about their earlier business dealings. Thus they were often easy prey to the argument that, for example, a donation to an observatory would assure them of posterity's favourable judgment. Why? Because such patronage would serve not only to advance scientific knowledge but to boost American prestige as well. Faith in science and the nation, as manifested in good works, would lead to social grace.

Miller, however, does not emphasize this part of the story. Instead, he concentrates on the scientist-salesmen whose initiative lay behind the laboratory boom in the United States, especially in the period 1870-1900. In the face of often great misunderstanding, these dedicated scholars exhibited great tenacity in the pursuit of funds for their work. Their larger vision was the institutionalization of basic research in universities and research institutes, in contrast to the pattern of Baconian, amateurish science which had prevailed during the earlier part of the century. Clearly they were successful, a fact which the author uses to demonstrate "what a small group with a dynamic programme could accomplish in the political and administrative underworld of scientific enterprise".

Yet the question remains as to what extent the character of the relationship between scientists and their patrons coloured the subsequent history of American science. While Miller does not deal with this point in any detail, his material does make informed specu-

lation possible. For instance, the link between appeals based on national prestige and the construction of the world's most expensive scientific apparatus was originally forged in the United States—among other places—during the Jacksonian era. Since then this theme has been realized more fully in America than anywhere else. With so many dollars available for so many telescopes and particle accelerators, is it any wonder that the style of "Big Science" owes historically more to America than to any other country?

PAUL GARY WERSKEY

Between World Tides

Marine Food Chains. Edited by J. H. Steele. Pp. viii+552. (Oliver and Boyd: Edinburgh, 1970.) 100s.

Marine Ecology. A Comprehensive, Integrated Treatise on Life in Oceans and Coastal Waters. Volume 1: Environmental Factors, Part 1. Edited by Otto Kinne. Pp. ix+681. (Wiley Interscience: London and New York, November 1970.) 250s.

BOTH these books are edited collections of papers dealing with marine ecology. There the similarity ends. Steele and his contributors take an analytical standpoint; they tackle a specific aspect of ecology—the food web—by considering natural events and processes in populations and ecosystems and then breaking them down into their component parts. At the opposite pole, Kinne and his colleagues start from the physical components of the environment (currents, temperature and light in this volume) and examine the impact of each one in turn on organs and organisms.

Steele's volume consists of the papers given at an international symposium; it leaves a clear impression, as symposia should, of what is not known and, therefore, of the kinds of research we ought to do next. Kinne's book is a collection of articles reviewing what is known; perhaps unintentionally, it leaves the reader with an overwhelming impression of the difficulty of synthesizing our knowledge of the components into an understanding of nature as a whole.

Marine Food Chains consists of twenty-nine papers given at a symposium in Aarhus in July 1968. They are assembled into six sections, each introduced by a distinguished authority in the subject. The titles of the sections illustrate the range: "Recycling of Organic Matter" (introduced by J. D. H. Strickland), "Pelagic Food Chains" (D. H. Cushing), "Feeding Mechanisms"

(C. B. Jørgensen), "Food Abundance and Availability in Relation to Production" (L. M. Dickie) and "Theoretical Problems" (J. H. Steele). There is a summary of the symposium by L. B. Slobodkin but the most effective summary is provided by Cushing's introductory sentence "Any supermarket shows the complexity of the simplest link in a food chain".

Many of the papers deal with the terminal yield of the marine food web and the significance of this in fisheries management. The symposium does not lead to any simple conclusion about the ecological efficiency of the food web; indeed, considerable doubt is cast on the oft-quoted figure of 10 per cent efficiency at each link. It is argued that models of food chains will depend on the recognition and understanding of functional rather than classical taxonomic groups. Variability between groups and regions is likely to be so fundamental that generalized models of wide application are unlikely to be realizable. Further progress will be largely dependent on increased studies of natural populations in the field and, as Slobodkin says, "the quality of work that is done in the field has increased markedly in the last 10 years". Although the papers destroy some of the old ideas about food chains, I agree wholeheartedly with the concluding remark of the book—"the level of sophistication demonstrated by the papers presented in this symposium gives every reason to hope for major intellectual breakthroughs in the future".

It is less easy to pass judgment on *Marine Ecology* because its 681 pages constitute only the first of three parts which together will form no more than Volume 1 of "Environmental Factors". Four further volumes are planned, and we are warned that some of these will also appear in several parts; they will deal with "Physiological Mechanisms", "Cultivation", "Dynamics" and "Ocean Management".

This first part of Volume 1 contains three chapters, the first being an introduction to oceans and coastal waters as life supporting environments. This is followed by two major chapters dealing with light and temperature (each with five authors). Each chapter is subdivided according to a standard scheme, starting with an introduction and followed by reviews of the responses to light or temperature of (i) bacteria, (ii) fungi and blue-green algae, (iii) plants, (iv) invertebrates and (v) fish. Within each chapter the topics include functional responses, subdivided into tolerance, metabolism, reproduction and distribution; and structural responses

under the sub-headings of size, external structures and internal structures.

There are author, taxonomic and subject indices, and each of the three chapters concludes with a comprehensive bibliography which will be invaluable to many readers; a rough calculation suggests that more than 1,800 scientific papers are cited.

The sub-title to the whole series is "A Comprehensive, Integrated Treatise on Life in Oceans and Coastal Waters". There seems little doubt, to judge from this first part, that the treatise will be comprehensive, but the success of the venture will depend on the extent to which it does indeed manage to integrate or synthesize the several parts and volumes into an ecological account. The present volume does not give grounds for confidence on this point. Indeed, the two chief factors dealt with here have been splintered in order to conform with the plan of the series. For example, the physiological and biochemical mechanisms of photosynthesis are excluded from the sub-chapter dealing with light in relation to plants. The account of light in relation to invertebrates also excludes a great deal of physiology and biochemistry which will be considered in later volumes along with topics such as morphology of photoreceptors, visual acuity, spectral sensitivity and bioluminescence. The venture on which Kinne has embarked is so large and ambitious that one must wonder whether the early volumes will be out of date before the final ones are published.

The charge that the book fragments ecology should not conceal its virtues; it is a major contribution to the literature of marine biology. Many of the sub-chapters are excellent reviews which will be read with great profit by students and research workers; I particularly liked N. G. Jerlov's short introduction to light in the sea, F. Gessner's and O. Kinne's sections on temperature in relation to plants and invertebrates, respectively, and J. H. S. Blaxter's sub-chapter on light in relation to fish.

In a treatise on ecology one expects a greater emphasis on populations and communities rather than organs and organisms but perhaps this will come in later volumes. The geographical aspects of ecology receive less attention than they deserve and the plankton gets less emphasis than the inshore and benthic organisms; but perhaps these are reflections of the need for more work on biogeography and plankton in relation to light and temperature.

These two books will be used in quite different ways. *Marine Food Chains* will be most useful to experienced research workers; it will be invaluable to those who are planning their future research programmes. *Marine Ecology* is likely to be more useful for senior

students and those just beginning their research careers but who among such people can afford at least seven and perhaps more volumes at the present price of 250s each? Both volumes, however, should find a place in the libraries of universities and research institutes where they will be thoroughly used.

R. S. GLOVER

Road to the Isles

Patterns of Highland Development. By David Turnock. Pp. xviii+272+32 plates. (Macmillan: London, July 1970.) 160s.

SINCE the setting up of the Highlands and Islands Development Board in 1965, it has been widely acknowledged that special measures are necessary to tackle the problems of this lagging region of Britain in a realistic way; much of the Board's work could be said to confirm a central conclusion of this book—that under-development has been due less to poor resources and peripheral location than to shortcomings in the way these have been put to use.

Mr Turnock has taken on and in large measure achieved a formidable task—to review comprehensively and in historical perspective the facts about resource use, industry, tourism, employment, population, communications and rural and urban settlements in all the diverse and changing patterns which these make in this region. Furthermore he has attempted to reach at least tentative conclusions about a development strategy; a policy in which the promotion of further growth of industry and services at principal centres like Invergordon in the east and south is balanced by smaller development within reach of nodal points in the crofting west and north. His argument is at times uneven and inevitably ends in questions which perhaps only those involved in regional development could answer more firmly in terms of current feasibilities.

He throws a well informed historical light on such questions, intriguing in hindsight, as why the importance of forestry as a lasting resource was not seen at the time of the Clearances, why commercial fishing came to be exploited mainly by east coast men rather than at the better natural harbours of the west which are nearer the fisheries, why nodal centres with widely based employment are still poorly represented in some sub-regions and why it has taken government so long to recognize that development cannot be limited to crofting agriculture and must be multi-purpose.

The story is informed by a wealth of field survey material, derived notably from the author's PhD thesis on Lochaber and stimulated, as he acknow-

ledges, by O'Dell and Walton's classic geography of the region and other sources which are listed in a valuable twelve page bibliography. Thirty-two aptly chosen and annotated plates, mostly oblique air photographs, constitute an integral part of the work, as do thirty-two maps and diagrams, some of which, however, are on too small a scale to do justice to their content.

This is a valuable textbook and general reference and will be essential reading for those wishing to understand the present stage of development in the largest of Britain's rural regions.

F. D. N. SPAVEN

Psychology of Behaviour

Brain Mechanisms and Behaviour. An Outline of the Mechanisms of Emotion, Memory, Learning and the Organization of Behaviour, with particular regard to the Limbic System. By J. R. Smythies. Second edition. Pp. vi+186. (Academic: New York, September 1970.) 61s.

IN a lucid and critical account of work on the limbic system, Dr Smythies outlines some physiological psychology and behavioural aspects of neurology for those clinical psychiatrists and neurobiologists to whom the brain is still merely a tissue.

The chief part of the first chapter has in eight pages an almost ideal prolegomenon for any newcomer to the study of brain mechanisms of behaviour—an array of qualifications and strictures on the interpretation of results using the present techniques. Nevertheless, of course, Smythies does not resist the temptation to try to make sense of the mass of available data. First he provides a digest of limbic system anatomy (with a few redundant diagrams, but otherwise unusually clear). Subsequent chapters summarize and attempt to integrate the results of selected experiments relating the behaviour of rat, cat, monkey and man to ablation, stimulation, macroelectrode recording and amine biochemistry. The contradictions and complexity are there, but the author is an admirable guide through the maze. He avoids behavioural and other jargon, although abbreviations often have to be decoded by context or by using a list found at the end of the chapter. Unit recording studies are hardly mentioned; studies of neuronal firing patterns in response to natural stimuli or in correlation with ongoing behaviour (with and without interference with the brain elsewhere) are very recent in the limbic system, however, and this book takes the literature up to 1968.

The book is, in fact, the second edition of *The Neurological Foundations of Psychiatry* (1966). The change of

title indicates, among other things, an introductory text suitable not just for psychiatrists but also for physiological psychology courses, and rather different from McCleary and Moore. The revision is chiefly addition of passages to the ends of some chapters (not always related to the original text). A separate list of review articles—a feature of the original edition useful in an introductory text—has disappeared. Curiously, the bibliography does not include Smythies, 1957 or 1963, cited in the text. Naturally, another author might have included or excluded some experiments or theories Smythies has not, especially if writing now, rather than two years ago. But, in my opinion, the treatment seems judicious and broadly up to date, and pleasingly detailed for an overall picture in so brief a compass.

One may doubt that all psychological explanations of normal human learning and thought must eventually be superseded by more powerful physiological explanations—making sense of otherwise arbitrary details of the microscopic workings of the brain is likely to require reference to functional control. Yet even if that is so, it is important to press on in the direction of Smythies's concluding "psychiatric speculations", and make them testable as he hopes. He suggests that in normal behaviour the limbic system selects ideation (and perhaps perception) according to emotional and motivational relevance. Then in endogenous depression and in schizophrenia, the limbic system may mediate the generation by affect of unrealistic thought and experience, respectively. Explaining cerebral control of behaviour is more than merely an intellectual challenge, daunting though that is.

D. A. BOOTH

Biology of Land Slugs

Terrestrial Slugs. By N. W. Runham and P. J. Hunter. Pp. 184. (Hutchinson: London, January 1971.) 40s boards; 16s paper.

Terrestrial Slugs is a volume in the Hutchinson's University Library series. It is clearly printed, easily read, and is superior to some of its companion volumes, for it has a comprehensive, modern and easily used literature list with the full titles of the references. It has also a considerable number of illustrations, but these are of a variable quality. In the preface the authors write that the book might "promote the use of slugs in schools and universities for research and teaching". It may well succeed in doing this, for certain chapters such as those on "Food", "Metabolism", and "Slugs as Pests" review the available information clearly and

simply and so make a definite contribution to the subject.

The other group for whom the book is intended are "people seeking to control . . . these pests" who might then produce "more effective chemical and biological control methods". This group is less well served for following this idealism one might expect after concluding in chapter 8 that biological control is at the present time impractical, the authors would then give a comprehensive review of the topic to preserve the balance of the book. In fact, biological control is dismissed in 100 words as an academic bauble and even slug predators have only about 400 words in the ecology section. The section on chemical control has ten times more space, and although this may reflect current thinking among those engaged in chemical control, I suspect that this may be changing quicker than the authors appreciate.

Certain topics like microhabitats, micrometeorology and a key to the mere twenty-six British species are not included and others, like taxonomy, genetics and behaviour, could either be expanded or improved. The ecology section, around which the whole book could have pivoted, is somewhat parochial in approach and is opened by a section on sampling methods where the usual distinction between mechanical and behavioural extraction techniques is not made. I found the authors provocative in the section on population regulation and not too helpful to the lay reader (at whom the book is aimed) who would require references to both Wynne-Edwards and Solomon. The authors do not review ecological energetics because "this . . . study does not help us to understand the distribution of a single species, or how the numbers are regulated" (p. 129). This valuable modern approach, which has given ecologists their first opportunity to evaluate the components of an ecosystem, is thus dismissed for not supplying the answers to questions not asked of it.

This book succeeds in surveying most aspects of the modern work on slug biology. It is a work of honest endeavour but proof reading errors and inaccuracies in the text leave scope for improvement in a subsequent edition.

PETER F. NEWELL

African Beetles

Monograph of the Praeugenina. (Coleoptera: Tenebrionidae: Strongyliini.) By P. P. de Moor. Pp. vii+203+8 plates and 8 maps. (The Transvaal Museum: Pretoria, 1970.)

DESPITE the richness and singularity of the beetle fauna of Ethiopian Africa,

comprehensive studies of the African fauna in particular groups of Coleoptera are still very few. The very large family Tenebrionidae has been studied in South Africa by C. Koch, who died after producing only one volume of a projected series on the South African representatives of the family; P. P. de Moor now seems to be carrying on his tradition in the Transvaal Museum, who are to be congratulated on this excellently produced publication.

The Praeugenina are limited to Africa and Madagascar, and comprise eleven currently recognized genera, five of which are confined to Madagascar and not treated in detail in this work; one of the six African genera, already monographed by Gridelli, is also not dealt with beyond inclusion in the key to genera. Five genera and some 107 species are fully characterized and illustrated by figures of whole beetles and aedeagi. As pointed out by de Moor, nothing has yet been recorded about the larvae, habitats and habits of any of the species, beyond the fact that most specimens in museum collections have been taken at lights.

In defining the group, de Moor says "The presence of a stridulatory gula distinguishes the subtribe Praeugenina from all other tribes of Tenebrionidae . . . excepting the Platynotini and Oncotini". This statement is incorrect, or at least misleading, as stridulatory files on the gula are found also in *Helops* spp., *Gnathocerus*, and some Hypophloeinae. He also draws attention to an additional character distinguishing Strongyliini from Tenebrionini, in the presence of a semi-transparent and partly sclerotized membrane fused to the anterior edge of the clypeus, and comments on the placings of a number of genera.

The author deals very briefly with "Distribution and Phylogenetic Considerations", saying "In view of the lack of knowledge regarding all but the superficial anatomy, not only of this group but of the entire subfamily Strongyliinae, it seems unwise at present to speculate on phylogenetic relationships", and is content to produce what the numerical taxonomists would call phonetically based groupings. This is not likely to detract from the immediate usefulness of his work.

In sum, this work represents a very useful and promising beginning; to treat the entire family Tenebrionidae of Africa alone on the scale set by Mr de Moor in this book would require thirty or more similar sized volumes, and might well occupy him for more than a lifetime. Meanwhile, there might be a case for the production of works dealing with larger groupings in a less thorough and detailed way, perhaps on the model of Schedl's on African Scolytidae.

R. A. CROWSON

Star Spectra

Spectroscopic Astrophysics. Edited by G. H. Herbig. Pp. ix+462. (University of California: Berkeley, Los Angeles and London, 1970.)

MEMORIALS to outstanding scientists can take different forms, one of the more familiar being those volumes written by former pupils which stress the great advances which have been made in fields opened up originally by the scientist to be remembered. Science moves so fast at present that it is rarely worth reprinting in their original form publications of earlier years, even those of pioneers. That it was possible, as has been done in the present memorial volume, to reprint with few omissions a number of papers originally published some thirty or more years ago testifies to the greatness of the man remembered, Otto Struve, who died in 1963. There are indeed few fields in astronomical spectroscopy which have not been fundamentally advanced if not actually inaugurated in one or the other of Struve's large number of publications.

Out of well over four hundred research papers, ten particularly striking samples, all very familiar to the older generation of astronomers, have been selected by J. L. Greenstein, G. H. Herbig and W. A. Hiltner, who had been charged by the American Astronomical Society with the task to prepare a fitting memorial to Otto Struve. The oldest of the reprinted papers, on the Stark effect in stellar spectra, dates back to 1929, and I vividly remember the impression which that paper created when Struve discussed it at the time before the members of the well known Physics Seminar of Berlin University.

G. H. Herbig, the editor of this remarkable volume, has let each of these Struve papers be followed by an expert's commentary which gives a present day view of developments in all those fields with which Struve's papers are concerned. The twelve authors of these commentaries, all former colleagues or associates of Otto Struve, are themselves sufficiently distinguished to make their essays on their own account amply merit publication. Struve's paper, published in 1933, on the problem of spectral classification is thus followed by a commentary by W. W. Morgan. Struve and Elvey's well known early paper on the curve of growth is succeeded by Greenstein's discussion of the method as it has been used in the thirty years since 1934. Struve's 1929 investigation of the Stark effect in stellar spectra is followed by a detailed discussion of the effect of Stark broadening on Balmer lines, given by E. Böhm-Vitense. Three papers which Struve wrote together with Wurm, Swings or Rudkjøbing on stellar envelopes, peculiar objects such as Z Andromedae and

the T Tauri stars have found detailed commentaries by Underhill, Swings and Herbig. Another well known paper by Struve on the composition of the interstellar medium is brought up to date by Münch and van de Hulst. In the early nineteen fifties Struve had taken a keen interest in the Beta Canis Majoris stars, and his paper is here discussed by van Hoof. A long commentary is devoted by Kraft to the problem of stellar rotation; this follows Struve's famous 1930 paper on the effect of rapid axial rotation on line profiles. The final paper in this volume deals very appropriately with spectroscopic binaries which were Struve's earliest interest and which remained of particular concern to him through all his life. The commentary in this case is by D. M. Popper.

In length, the commentaries vary from two to nearly forty pages. Herbig as editor has refrained from forcing contributors to stick to the same length or even the same pattern in their commentaries. In this way he has produced a lively and eminently readable book which conveys in a unique way an excellent picture of a remarkable man who achieved what he did because, obviously, nothing mattered to him but astronomy. Apart from its importance to anyone concerned with astrophysical spectroscopy the book will give great pleasure to the many who came to know and admire Otto Struve and his work.

H. A. BRÜCK

Test for Contamination

Environmental Surveillance in the Vicinity of Nuclear Facilities. Edited by William C. Reinig. (Proceedings of a Symposium sponsored by the Health Physics Society.) Pp. xvi+465. (Thomas: Springfield, Illinois, July 1970.) \$29.

THE contents of this book are very relevant to the efforts now being made to prevent deterioration in the environment and hazard to man as a result of current technological development. The book contains an interesting collection of papers presented at a symposium of the Health Physics Society in the United States in January 1968. The claims in the preface that the book presents an international viewpoint are sustained by the participation of 15 authors from seven countries, not counting the considerable number from America. The 46 papers are divided amongst five topics. The first of these concerns the objectives of environmental surveillance, and three papers are presented by authors from Britain, America, and Canada respectively. This section is based substantially on the recommendations of the International Commission on Radiological Protection, contained in its Publication Seven on *Principles*

of *Environmental Monitoring*. Emphasis is placed on the need to monitor materials which have close proximity to man, and for clear scientific objectives.

A substantial section of the book is concerned with the design and methods of environmental surveillance in normal operations and in emergency situations. The protection of man from exposure to ionizing radiation is, of course, the primary objective, and in one section of the book seven papers are presented on the dose to populations determined from actual experience in the operation of nuclear facilities. The actual doses received by people in the instances given are relatively very small and, even on pessimistic assumptions of the risks from ionizing radiation, the consequences to the populations involved would be negligible.

One interesting paper in this section reviews the recommendations of four international agencies: the International Commission on Radiological Protection (ICRP), the International Atomic Energy Agency (IAEA), the Food and Agriculture Organization of the United Nations (FAO), and the World Health Organization (WHO). While the ICRP contribution provides the fundamental principles and information on the significance of radiation exposure, a joint paper from the three other agencies is the best reference for radiochemical methods and evaluation and the use of instruments. Both the IAEA and the WHO underline the importance of scientists planning the surveys, and the WHO emphasize the importance of cooperation between operator and the health authority in ensuring a satisfactory environment.

Perhaps the most interesting part of the book is the fifth section, concerned with research in support of environmental surveillance. Some of the papers in this section present data derived from the escape of fission products in experiments with nuclear rockets, but most of the data relate to experience in the development of nuclear power, including the behaviour of radiostrontium in streams, of tritium in air and soil, and of radioiodine on pastures and in milk. Other papers deal with the calculation of doses to various organs from inhaled fission products and with the calculation of doses from gamma spectrometer measurements in environmental surveys.

This book demonstrates the wide extent of the knowledge and experience available regarding the behaviour of radioactivity in the environment and the passage through food chains to man. While much of the information will be well known to the professional health physicist, the book may reassure the layman about the protection of human beings in the vicinity of nuclear facilities.

W. G. MARLEY

CORRESPONDENCE

Fungus Research

SIR,—It is becoming increasingly obvious that diseases of fungal origin are of major importance. The use of cytotoxic and immuno-suppressive drugs, corticosteroids and broad spectrum antibiotics is leading to an increasing number of local and generalized mycotic infections. The need for control of non-bacterial infections in extensive—for example, open heart—surgery is a major problem. Even dermatophyte infections are responsible for serious morbidity and wastage of man-hours. In industry, for instance, there were more than 5,000 spells of incapacity attributable to dermatophytosis from June 1967 to June 1968. The average length of absence from work was 13 days and a total of more than 111,000 man-days was lost (Department of Health and Social Security, 1969). In the veterinary field, mycotic abortion and *Dermatophilus* infection are also of considerable economic importance.

In order to gain some information concerning the amount of work being done in the United Kingdom in the field of medical and veterinary mycopathology, the Medical Mycology Subcommittee (disbanded 1969) of the Medical Research Council sent a questionnaire and a letter explaining the aims to a number of centres and individuals. The distribution list was compiled on the basis of persons known to be associated with the subject, either because of their membership of the British Society for Mycopathology or because of their personal contact with members of the Medical Mycology Committee. In fact, almost all of the medical teaching centres in the country and the majority of veterinary teaching establishments were included. The results of this were communicated to the MRC which has since given mycology a high priority. The main points elucidated are set out as follows.

Of 87 replies received out of 92 questionnaires sent out, 10 were from departments or sections employing at least one trained mycologist. All were engaged in research, a diagnostic service was provided by 8 and teaching was carried out in 6.

Replies from 34 medical centres (dermatological, bacteriological and pathologic departments) indicated that although teaching was carried out in the majority this was mainly clinical and in dermatology departments. Of the 34 replies from veterinary establishments (largely ARC sponsored units) 33 offered a diagnostic service but only 8 and 7 centres also contributed to teaching and research respectively. It was clear that medical mycology was taught piece-

meal to medical and veterinary students (one or two lectures) and hardly ever to science students.

The survey also emphasized that there is a remarkably small number of persons employed in medical and veterinary mycology. This was confirmed by reference to membership list of the British Society for Mycopathology. Of the 83 British members only 31 had received formal training in mycology and of these 9 were young individuals still under training.

One of the elements involved in this unsatisfactory situation is the lack of a firm career structure for medical mycologists. Implementation of the Zuckermann report in the NHS might alleviate this but nevertheless the training of more medical mycologists is essential.

A place should be found in undergraduate curricula in science and medicine for more extensive teaching in medical mycology, and the institution of an MSc course would also be of the utmost value. In this way, a supply of adequately trained workers for university and hospital departments would become available and thus provide a better mycological service throughout. Fundamental research would also be stimulated and would have an influence beyond mycology itself. The fungi provide excellent systems for the study of the general problems of host-parasite relations and there is no lack of subjects which urgently require direct investigation.

Yours faithfully,

J. T. INGRAM

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University of Newcastle*

C. N. D. CRUICKSHANK

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Transferrin

SIR,—In a recent *Nature* article¹, Chernelch and Brown concluded that their *in vivo* experiments designed to test the Fletcher-Huehns hypothesis of functional differences of iron atoms bound to transferrin² failed to support the predictions of this theory. These authors apparently have overlooked or misinterpreted two earlier publications which indicate that an exchange of iron atoms occurs among molecules of transferrin and apotransferrin. Morgan *et al.*³ have shown that *in vivo* experiments in

humans “provided evidence for the return to the plasma of appreciable amounts of radioiron attached to a second transferrin”. Aisen and Leibman⁴ demonstrated that at physiological concentration of citrate and at pH 7.4, there was complete and rapid exchange of iron atoms between transferrins and apotransferrins. In light of this evidence it is difficult to understand how Chernelch and Brown could be able to follow the course of transferrins selectively labelled predominantly on sites A or B of transferrin molecules in an *in vivo* study wherein exchange would occur. The failure of their experiments to behave in the predicted manner does not invalidate the Fletcher-Huehns theory as they have suggested.

As a criterion for their hypothesis, Fletcher and Huehns postulated that there be no redistribution of iron from one binding site to another. This is not a mandatory dictate for their theory. If iron exchange among transferrin molecules is mediated by a low molecular weight chelating agent such as citrate, possibly by the formation of a ternary complex⁵ or if the exchange is due to feedback from a second reflux compartment of the iron pool³, then even in the event of complete equilibrium of iron transferrin binding site exchange, there still will be equal numbers of molecules with iron bound to either site and metabolism would be regulated by the number of receptors and their rates of reactivity.

Yours faithfully,

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¹ Chernelch, M., and Brown, E. B., *Nature*, **226**, 356 (1970).

² Fletcher, J., and Huehns, E. R., *Nature*, **218**, 1211 (1968).

³ Morgan, E. H., Marsaglia, G., Giblett, E. R., and Finch, C. A., *J. Lab. Clin. Med.*, **69**, 370 (1967).

⁴ Aisen, P., and Leibman, A., *Biochem. Biophys. Res. Commun.*, **32**, 220 (1968).

⁵ Bates, G. W., Billups, C., and Saltman, P., *J. Biol. Chem.*, **242**, 2810 (1967).

Meat Factories

SIR,—For several reasons, the practice of killing animals for their meat may well become more and more impractical in the future. There is a moral standpoint, for instance, from which one perhaps ought not to eat meat if one is not at least prepared to kill the animal personally; however, vegetarianism seems a dubious (not to say unsatisfactory)

proposition to most people, who will successfully ignore this moral point and continue to insist on meat as long as it is available. It may not be available indefinitely, however; as the world's population increases, there must come a point where industry will cast an unromantic eye at cow pastures, sheep paddocks and other such inefficient institutions, and will insist on building something useful there.

My own research field is not a biological one, and the following may not be very practical but, I believe, ought to be given some thought: have tissue-culture specialists thought of applying their techniques to the culturing of edible animal tissues? A number of advantages over conventional animal culture spring to mind, the most important one perhaps the fact that, theoretically at least, one should be able to produce more "meat" in a given volume or area than by sending cows out to graze (even if the American cattle industry continues to rationalize its business). The technical problems and costs involved may well be tremendous, but this will become less and less relevant as the population increases. The anti-killing moralists would concede, I think, that a mass of cultured animal tissue is (except nutritionally) little different from cultured plant tissue (the hidden moral point—that, given an increasing human population density, we will eventually not be able to allow other animals much space—may be conveniently ignored here).

If the technical problems are soluble, there would be gastronomic advantages in this—there seems to be no reason why one should not culture a vast variety of "meats"; there will be no such thing as a rare and costly tissue—although it is doubtful that this "meat" would turn out like the fibrous stuff we eat now.

I envisage meat factories for the year 2000.

Yours faithfully,

D. BRITZ

Jülich,
Germany

Multiple Authorship

SIR,—In this day of "publish or perish" one increasingly encounters papers authored by several persons. A high percentage of team work, and thus a high percentage of multiple authorship, can, in fact, be considered a reflexion of the state of advancement of a particular science¹. The January 30, 1970, issue of *Science*² reporting on the scientific results of the Apollo 11 moon expedition is an excellent though exceptional case in point. In this issue there were 144 papers authored by a total of 619 persons, an average of 4.3 authors per paper. One paper was by 18 authors (is this a record?), two other papers by 14 authors each, one by 12, and two by 11 each; at

the other extreme, ten papers were authored by only one person. Merely the names and addresses on the paper with 18 authors required five column inches of space.

The very number of publications listed in a bibliography of a scientist often gives an inflated estimation of the scientific contribution of that person. Obviously more entries are possible if a person participates in a great deal of team work. What is needed is some method to rate the equivalent value of a scientific paper authored by several persons. Each paper, no matter by how many authors, should count as unity (one equivalent paper). That is, the paper with 18 authors, if listed in bibliographies by each of the 18 authors, should count as one paper total, and not 18. The following table presents sample equivalent values for papers with up to six authors:

Paper authored by:	Values of equivalent papers per author					
	A	B	C	D	E	F
A	1.00					
AB	0.67	0.33				
ABC	0.50	0.33	0.17			
ABCD	0.40	0.30	0.20	0.10		
ABCDE	0.33	0.27	0.20	0.13	0.07	
ABCDEF	0.29	0.24	0.19	0.14	0.09	0.05

For example, three papers individually authored by "X" (total of 3 equivalent papers) are "worth" slightly more than six papers authored by "Y" as follows: Y, YB, YB, AY, ABY, ABCY (total of 2.94 equivalent papers), even though "Y" has twice as many publications as "X".

There are two possibilities for situations with six or more authors per paper since the contribution of the sixth and additional authors ranges from $1/21$ to $1/\infty$ (euphemism for essentially zero: for example, the contribution of author number 18 is $1/171$ or 0.006 equivalent paper): (1) the contributors in excess of five might well (preferably!) be relegated to acknowledgment status in a footnote, or (2) they might be listed alphabetically (as is currently done with the more notable movie stars in epics).

A final plea: in personal bibliographies of scientists, entries for papers by several authors should include a list of the authors in the sequence they appear on the paper. Thus, in a bibliography for author "Y" a paper by "ABY" should be cited as "by ABY" and not, as is so commonly done, as "with AB", since the latter gives no indication of the ranking of the authors (and who did all the work). I leave it to other workers to develop more exact and complex relationships taking into consideration other significant variables (length, type of paper (for example, taxonomic monograph, review paper), etc.).

Yours faithfully,

RUDOLF SCHMID

Department of Botany,
University of Michigan,

Ann Arbor,
Michigan 48104

¹ Manten, A. A., *Earth Sci. Rev.*, **6**, 181 (1970).

² *Science*, **167**, 417 (1970).

Cycles in Behaviour

SIR,—The whole approach of analogizing between the natural sciences and the behaviour of human society could well distinguish itself only by its naivety. Nevertheless, history is strewn with examples of the fertility of cross-disciplinary activities, and at least one Great Man has urged us to "only connect".

Young and Ziman (*Nature*, **229**, 91; 1971) concern themselves with establishing a nomenclature to facilitate discussion of cycles in social behaviour, by borrowing terms from physics. This they do very convincingly except that they do not make the important distinction between an oscillating function of time and a periodic function of time. An oscillating function is normally understood to be one which exhibits a sequence of turning points: thus one speaks of super-critically and sub-critically damped harmonic motion, where the former exhibits a monotonic trend toward some asymptote and is non-oscillatory, and the latter is oscillatory but not periodic. A periodic function would exhibit a waveform that is exactly repeated over intervals of the period.

The distinction between oscillations with regularly spaced turning points and periodic motion vanishes when the ordinate is non-numerable in the sense that an event can only be said to occur or not occur, for then only the intervals between events matter. However, there clearly exist cases where more quantification of a social variable is possible. For instance, as the authors point out, historical events sometimes display temporal influences that decay in a manner suggestive of a relaxation time. The "modulation" of a periodic function such as the yearly religious festivals by a decaying historical influence could clearly result in an oscillating social variable that is aperiodic.

Perhaps it is sometimes appropriate in discussing the behaviour of human society to use a logarithmic rather than a linear scale of time. The significance to us of a fixed interval of time seems to depend on average roughly how long ago that interval is placed. This follows if events have relaxation times. The "larger" the event and/or the longer its relaxation time the longer its significance: the memory we now have of some interval in history depends on the sum of its remnant influences, and the farther back the interval the less cause, on average, we now have to remember it. History, archaeology, geological eras, scientific papers, personal experience and future forecasting all seem to imply a roughly

logarithmic concept of time ahead and time past.

The existence of relaxation times follows both from a subsequent accommodation by society of the effects of a

historical event, and from failing memory. Clearly these two causes are not always distinct.

Yours faithfully,
BARRIE W. JONES

CRSR,
Cornell University,
Ithaca,
New York

Obituary

C. V. Raman



MODERN science started taking root in India only in recent times. Sir Chandrasekhara Venkata Raman, who died in November at the age of eighty-two, was the outstanding figure during the last half century in this renaissance and, in more than one sense, he may be regarded as its originator and leader. Great as his personal contributions to science have been, greater have been his achievements in training and inspiring a large number of brilliant, self-reliant and distinguished Indians who have made significant contributions not only to pure physics but also to areas such as meteorology, seismology, geology, soil physics and mathematical physics. It is common knowledge that Raman himself had no training in foreign laboratories. He started his scientific career without any external stimulus and attained great eminence by his own individual effort. Many of his pupils and associates did likewise. The fact that they had built up flourishing and distinctive research schools without relying too much on foreign assistance reveals the profound influence exerted by the great leader on his colleagues.

He was born at Trichinopoly in south India in 1888 and was educated at the Hindu College, Visakhapatnam, where his father was professor of mathematics, and at the Presidency College, Madras. Even as an undergraduate, Raman did original work in acoustics and in optics, and his first scientific publications appeared as early as 1906 in *Nature* and in the *Philosophical Magazine* when he was in his eighteenth year. In the decade that followed, by a strange turn of events, he was an officer of the Indian

Finance Department till 1917, but kept up scientific interests, studying the dynamics of vibrations and sound, and the theory of musical instruments. Those early studies culminated in his publishing in 1918 an article of some 158 pages dealing with the theory of the musical instruments of the violin family. He also contributed some years later an article on the theory of musical instruments to the *Handbuch der Physik*.

The year 1921 was important in his scientific career, as then began his work on the scattering of light. By 1924 he made significant contributions and was invited to open a symposium on the scattering of light at the Toronto meeting of the British Association. In fact, his researches in the seven years that followed dealt with different aspects of the scattering of light and led to the discovery early in 1928 of the phenomenon that now bears his name—the Raman effect. The effect can be seen when monochromatic light is diffused or scattered by matter. It occurs because, while most of the scattered light has the same frequency as the incident light, a definite fraction undergoes a change in frequency by exchanging energy with the matter.

While the discovery of this phenomenon was his outstanding contribution during the many years of his scientific work, he made significant contributions to allied areas such as ultrasonics, diffraction of light, photoelasticity, X-ray diffraction, magnetism and magneto-crystalline action, electro and magneto-optics, crystal dynamics and so on. He also had a deep and aesthetic appreciation of nature and a scientific interest in the colours of birds, beetles and butterflies that evolved, in his later years, into a study of the colours of flowers and other natural objects. In addition, he made extensive contributions to the physics of vision and human hearing.

To realize the impact of the discovery of the Raman effect on the subject of physics as a whole, one should note that with the more recent discovery of the laser, the Raman effect has again become an area of great interest to physicists. The laser has introduced a new age of excitement in the field of light scattering, one in which it has become possible to study issues only accessible to strong sources of illumination such as those provided by lasers and in which a new effect has appeared, the Laser-Raman effect.

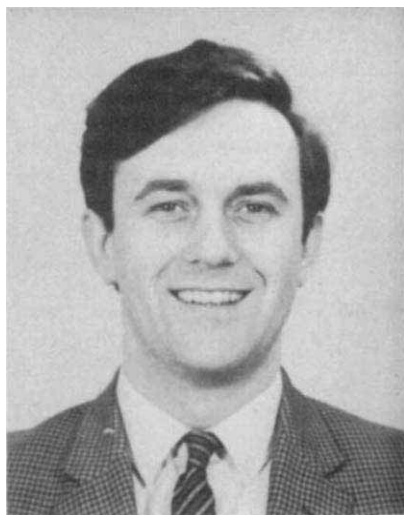
Honours were showered on Pro-

fessor Raman during his lifetime. They are too numerous to be cited here. Honorary degrees from universities, fellowships from learned societies and medals and certificates from scientific institutions of many countries were received by him in large numbers, indicating the brilliance and originality of his researches, the truly international character of the recognition which his work received and the permanent place which his contributions have earned for him in the history of world science. He was awarded the Nobel Prize for Physics in 1930, two years after he discovered the Raman effect.

But for a brief period of about ten years during which he served as an officer of the Indian Government, he devoted all his life and all his energies to fulfilling his one ambition which was to secure a prominent place for India on the scientific map of the world. He has succeeded in a fair measure in achieving this objective. His singular and unswerving devotion to science, his uncompromising attitude towards any attempt made to draw him out of his chosen path, his refreshingly independent way of looking at things, his unique ability to expound intricate scientific discoveries to large audiences and, above all, his fine and delicate sense of humour are so well known, that his colleagues who knew him intimately admired him as much for these qualities as they admired him for his contributions to science. Many institutions and universities in India have benefited by his influence, advice and support. He was the Founder President of the Indian Academy of Sciences and continued to be its president till his death. In that capacity, he was looking after the Proceedings of the Academy, which were published with unflinching regularity during the past forty years. He was also the president of *Current Science*, a fortnightly journal published from Bangalore.

After retirement from the Indian Institute of Science, he worked at the Raman Research Institute in Bangalore, an institute founded by him and to which he gave all his property including the money he received with the Nobel award. The Raman Research Institute today houses, among other things, an unusual collection of precious stones, gems and other rare items of great scientific interest and value. The institute together with the traditions which he established remain as his great legacy.

Professor R. K. Ham



THE death of Ron Ham in a car accident on November 13 has robbed the Open University of one of its brightest talents. Ham had been appointed professor of materials science in April 1970 and his enthusiasm for teaching coupled with imagination and wide experience had already laid sound foundations on which he and others were starting to build. In particular, he had a clear vision of the role and importance of technology and had successfully emphasized the necessity of direct cooperation with the "pure" sciences within the university. Ham was also winning real support from industry to assist in preparation and presentation of relevant course material. He reached

out far beyond his professorial specialism and indeed his last manuscript is a characteristically lively "Case Study" of the Electricity Supply Industry for the 1972 technology course. Ham was also deeply concerned to create opportunities for experienced scientists and engineers to keep abreast of developments in science, technology and industry.

All this high promise was founded on considerable achievements in metallurgy and materials science. Ham, a Canadian citizen, had been trained in engineering physics in Toronto, specializing in metallurgy. An Athlone fellowship brought him in 1955 to the Department of Industrial Metallurgy, Birmingham, where he began a series of investigations on the fatigue of metals which established him as a leading authority. His initial work, published in the *Proceedings of the Royal Society*, was on pure copper, followed in later years and in other laboratories with work on age-hardening alloys, ordered alloys and composite materials. Throughout this work, Ham showed a keen awareness of the practical implications of basic research and of the appropriateness of "enlightened empiricism" in tackling some complex industrial problems. After four years at Birmingham, Ham had a brief period at the Cavendish tackling a theoretical problem on the configuration of dislocations, inevitably becoming enthusiastic about direct observations of dislocations by transmission electron microscopy. During the following three years in Australia at the Division of Tribophysics of CSIRO, Ham tackled a problem that was being

sidestepped elsewhere, namely, the extent to which dislocations rearrange themselves or disappear during preparation of thin foils from bulk metal.

Ham returned to Canada in 1962, to a staff appointment at McMaster University. There he undertook a heavy teaching load with a wide diversity of students and topics. He enlarged his research interests, with high temperature creep starting to displace fatigue as his major field. From 1966 to 1970 at CERL Leatherhead, where he eventually became head of the Materials Division, Ham developed important new insights into the creep resistance of commercial steels and nickel-based alloys, and defined a completely new principle for the design of a useful class of creep-resisting alloys. Simultaneously, there was deep involvement in the solution of immediate technical problems of the CEBG, and, in what spare time he had, the preparation of a first-class review of age-hardening mechanisms.

Only a few of Ham's publications bear his name alone: his personality was such that he attracted others to share his enthusiasms and he readily gave them credit for what often seemed minor contributions. Throughout the world, those who knew the stimulus of his agile mind with its store of well-ordered information pay tribute to Ron Ham, not only as one of the leading materials scientists of his generation, but to a friend whose warmth and charm radiated a zest for living that enriched them all. Professor Ham was 37; he leaves a widow, Jane, and two young sons.

Announcements

Appointments

Dr William E. Paul has been appointed chief of the Laboratory of Immunology of the **US National Institute of Allergy and Infectious Diseases**.

The Governing Body of the **Lister Institute of Preventive Medicine** has elected **Professor A. Neuberger**, St Mary's Hospital, as chairman in succession to Sir Lindor Brown.

International Meetings

March 8-12, **Biophysical Aspects of Radiation Quality**, Lucas Heights, Australia (IAEA, Kärntnerring 11, PO Box 590, A-1011 Vienna, Austria).

March 29-April 2, **Use of Radiation and Radioisotopes for Genetic Improvement of Industrial Microorganisms**, Vienna (IAEA, Kärntnerring 11, PO Box 590, A-1011 Vienna, Austria).

March 29-April 2, **Psychosomatic Medicine in Obstetrics and Gynaecology**, London (Kurt Fleischmann and Associates, Chesham House, 136 Regent Street, London W1).

March 30-April 3, **Joint Annual Meeting of the Chemical Society and the Royal Institute of Chemistry**, Brighton (Dr John F. Gibson, The Chemical Society, Burlington House, London W1V 0BN).

March 31-April 2, **Genetical Society Meeting**, Cambridge (Professor D. A. Hopwood, John Innes Institute, Colney Lane, Norwich NOR 7OF).

April 13-17, **AGM of the Association of Teachers of Mathematics**, Lancaster (Executive Office, ATM, Market Street Chambers, Nelson, Lancashire).

April 14-16, **Teratology**, Cardiff (Dr J. B. Lloyd, Department of Biochemistry, University College, Cardiff, Wales).

April 19-22, **Process Instrumentation in the Metals Industry**, Swansea (The Secretary, Institute of Measurement and Control, 20 Peel Street, London W8 5BR).

April 19-23, **Magnetohydrodynamic Electrical Power Generation**, Munich (IAEA, Kärntnerring 11, PO Box 590, A-1011 Vienna, Austria).

April 21-22, **Advances in Concrete**, Birmingham (Operations Department, The Concrete Society, Terminal House, Grosvenor Gardens, London SW1).

April 26-29, **Circadian Rhythmicity**, Wageningen (International Agricultural Centre, PO Box 88, Wageningen, The Netherlands).

May 10-15, **Nuclear Ships**, Hamburg (IAEA, Kärntnerring 11, PO Box 590, A-1011 Vienna, Austria).

June 8-11, **Electrostatics**, Albany, New York (Professor A. D. Moore, Department of Electrical Engineering, University of Michigan, Ann Arbor, Michigan 48104, USA).

June 14-18, **Precambrian Metavolcanic and Plutonic Rocks of Colorado and Northern New Mexico**, New Mexico (F. Barker, US Geological Survey, Federal Center, Denver, Colorado 80225, USA).

June 17-23, **Plasma Physics and Controlled Nuclear Fusion Research**, Madison (IAEA, Kärntnerring 11, PO Box 590, A-1011 Vienna, Austria).

July 5-9, **Rapid Methods for Measuring Radioactivity in the Environment**, Munich (IAEA, Kärntnerring 11, PO Box 590, A-1011 Vienna, Austria).

July 18-22, **Wildlife Disease**, Falmer, Sussex (Dr A. McDiarmid, ARC Institute for Research on Animal Diseases, Compton, Newbury, Berkshire).

British Diary

Monday, February 8

Absorption of Hydrocarbons on to Oxide Surfaces Related to Road Building Materials (5.50 p.m.) Mr D. M. Colwill and Dr P. C. Thompson, Society of Chemical Industry, at 14 Belgrave Square, London SW1.

Effects of Rotor Eccentricity on Acoustic Noise from Induction Machines ; and Natural Frequencies of Stators of Small Electric Machines (5.30 p.m.) Dr A. J. Ellison and Dr S. J. Yang, Institution of Electrical Engineers, at Savoy Place, London WC2.

On the Nature of Linguistic Evidence (5.30 p.m.) Dr P. Seuren, British Society for the Philosophy of Science, in the Joint Staff Common Room, University College London, Gower Street, London WC1.

Stored Program Control Application in Telephone Switching (5.30 p.m.) Mr N. Ward, Institution of Electrical Engineers, at Savoy Place, London WC2.

Tuesday, February 9

A Personal View of Animal Behaviour (5 p.m.) Sir Frank Fraser Darling, University of London, at the Royal Veterinary College, Royal College Street, London NW1.

Compositional Changes of Solvent Mixtures during the Film Formation Process (7.30 p.m.) Mr L. A. Tysall and Dr D. H. Shearer, Oil and Colour Chemists' Association, at the Griffin Hotel, Boar Lane, Leeds.

Earthquakes (1.20 p.m.) Dr S. A. F. Murrell, University of London, in the Botany Theatre, University College London, Gower Street, London WC1.

Gas Turbines in Transportation (7.30 p.m.) Mr Noel Penny, Society of Environmental Engineers, in the Mechanical Engineering Department, The University, Birmingham.

Metabolism of Plasma Lipoproteins (5.30 p.m.) Dr B. Lewis, University of London, at the Institute of Child Health, 30 Guilford Street, London WC1. (Tenth of fifteen lectures on "The Scientific Basis of Medicine" organized by the British Postgraduate Medical Federation.)

Seals and Gaskets (6 p.m.) Dr G. P. Blair and Dr M. B. Johnston, Institution of Mechanical Engineers, at 1 Birdcage Walk, London SW1.

Waves and Vibrations (5.30 p.m.) Professor R. King, Royal Institution, at 21 Albemarle Street, London W1. (Lecture for Fourth Form pupils from Schools in London and the Home Counties. To be repeated on February 10, 16, 17 and 18.)

Wednesday, February 10

Concorde Electronics (6 p.m.) Mr H. Hill, Institution of Electronic and Radio Engineers, at 9 Bedford Square, London WC1.

Extrapolation of Creep, Strain and Rupture Properties of $\frac{1}{2}\% \text{Cr}$, $\frac{1}{2}\% \text{Mo}$, and $\frac{1}{4}\% \text{V}$ Pipe Steel (6 p.m.) Mr W. M. Cumming and Mr R. H. King, Institution of Mechanical Engineers, at 1 Birdcage Walk London SW1.

Food and the Control of Body-weight (6.15 p.m.) Dr R. Passmore, Society of Chemical Industry, at 14 Belgrave Square, London SW1.

Design and Constructional Techniques for Microelectronic Equipment (5.30 p.m.) Mr F. A. Robertson, Institution of Electrical Engineers, at Savoy Place, London WC2.

Hyperbolic Navigation Systems (6.30 p.m.) Mr C. Powell, Institution of Electronic and Radio Engineers, at Chelmsford Civic Centre, Chelmsford, Essex.

Modern Methods of Paint Application (3 p.m.) Mr K. Baxter, Oil and Colour Chemists' Association, Newcastle Student Group, at Newcastle Polytechnic, Ellison Place, Newcastle upon Tyne.

Optimisation of Non-linear Dynamic Systems (5.30 p.m. discussion) Institution of Electrical Engineers, jointly with the Institute of Measurement and Control, at Savoy Place, London WC2.

Roberts-Austen's "Introduction to the Study of Metallurgy", 1891 (1 p.m.) Mr C. C. Moore, Royal Institution, History of Science Discussion Group, at 21 Albemarle Street, London W1.

Testing of Commercial Vehicles (6 p.m.) Mr A. Oates, Society of Environmental Engineers, in the Mechanical Engineering Department, Imperial College, London SW7.

The Calcitonins (4.30 p.m.) Professor D. H. Copp, Medical Research Council, at the National Institute for Medical Research, Mill Hill, London, NW7.

The Changing Technology of Coal Extraction (6 p.m.) Mr G. W. Sanders, Royal Society of Arts, at John Adam Street, London WC2. (Cadman Memorial Lecture.)

The Teaching of Analytical Chemistry in the USA—Do We have Anything to Learn? (6.30 p.m. discussion) Society for Analytical Chemistry, at the University, Birmingham.

Thursday, February 11

Haemostatic Functions of Platelets and their Disorders (5.30 p.m.) Professor R. M. Hardisty, University of London, at the Institute of Child Health, 30 Guilford Street, London WC1. (Eleventh of fifteen lectures on "The Scientific Basis of Medicine" organized by the British Postgraduate Medical Federation.)

Marketing and Electricity (5.30 p.m.) Mr J. W. Hobson, Institution of Electrical Engineers, at Savoy Place, London WC2.

On Line Data Capture and Verification (2.30 p.m. colloquium) Institution of Electronic and Radio Engineers, Joint IEE/IERE Computer Group, at the IERE, 9 Bedford Square, London WC1.

Properties of Matter. Part 3: Metals. Part 4: Plastics and Rubbers. Part 5: Surfaces (1 p.m. films) Royal Institution at 21 Albemarle Street, London W1.

Steric Hindrance in Analytical Chemistry (7 p.m.) Professor H. M. N. H. Irving, Society for Analytical Chemistry, jointly with the South Wales Section of the RIC, in the Department of Chemistry, University College, Swansea.

The Implications of Noise in Hydraulic Systems (4.15 p.m. discussion) Institution of Mechanical Engineers, at 1 Birdcage Walk, London SW1.

Friday, February 12

Developments in Transmission and Distribution Sub-station Control and Instrumentation (5.30 p.m. discussion) Institution of Electrical Engineers, at Savoy Place, London WC2.

Electrical Transducers for Measurement of Mechanical Quantities (11 a.m. colloquium) Institution of Electrical Engineers, jointly with the I.Mech.E., and the Inst.M.C., at Savoy Place, London WC2.

Present and Future Trends in Motor Car Finishing (6.30 p.m.) Mr H. L. Quick, Oil and Colour Chemists' Association, at the Manchester Literary and Philosophical Society, 36 George Street, Manchester 1.

Radiation Mechanisms in Pulsars and the Magnetosphere of a Rotating Neutron Star (2 p.m. discussion), Royal Astronomical Society, at Burlington House, Piccadilly, London W1.

Solid and Liquid Metals (9 p.m.) Professor C. C. Addison, FRS, Royal Institution, at 21 Albemarle Street, London W1.

Spectroscopic Properties of Biferrocene Fe(II) Fe(III) Picrate (1 p.m.) Dr F. Kaufman, Royal Institution, Photochemistry Discussion Group, at 21 Albemarle Street, London W1.

Sporadic Outbursts of Red Dwarf Stars (4.30 p.m.) Professor Sir Bernard Lovell, OBE, FRS, Royal Astronomical Society, at Burlington House, Piccadilly, London W1. (Presidential Address.)

Saturday, February 13

A City of the Ancient Maya—Recent Excavations at Lubaantun, Belize, British Honduras (3.30 p.m.) Mr Norman Hammond, Inner London Education Authority, at the Horniman Museum, London Road, Forest Hill, London SE23.

Monday, February 15

Pumps for High Viscosity Fluids (6 p.m. discussion) Institution of Mechanical Engineers, at 1 Birdcage Walk, London SW1.

Science and Anti-Science (8 p.m.) Professor I. Lakatos and Dr Jerry Ravetz, British Society for Social Responsibility in Science, at the Institute of Contemporary Arts, Nash House, The Mall, London SW1.

Science in Fleet Street (5.30 p.m.) Dr A. R. Michaelis, Royal Institution, Library Circle, at 21 Albemarle Street, London W1.

The Function of the Cytochrome System and Related Redox Chain Components in Bacteria and Mitochondria (5.30 p.m.) Dr Peter Mitchell, University of London, in the Botany Theatre, University College London, Gower Street, London WC1.

The Search for More Effective Rodenticides (10.30 a.m. symposium) Society of Chemical Industry, at 14 Belgrave Square, London SW1.

Trainable Computer Programs for Circuit Design (5.30 p.m.) Mr G. C. Brown, Institution of Electrical Engineers, at Savoy Place, London WC2.

Reports and Publications

not included in the monthly Books Supplement

Great Britain and Ireland

County Borough of Hastings. Annual Report of the Medical Officer of Health, Chief Welfare Officer, and Principal School Medical Officer for 1969. Pp. 116. (Hastings : Health Department, County Borough of Hastings, 1970.) [2112]

Bulletin of Special Courses in Higher Technology, Management Studies and Commerce, 1970/1971. Part 2 : Spring and Summer Terms. Pp. 116. (London : London and Home Counties Regional Advisory Council for Technological Education, 1970.) 10s. [2112]

National Physical Laboratory. SI Units in Electricity and Magnetism. By G. H. Rayner

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Will contributors to *Nature* follow as far as possible the general style of the journal, and in particular the following rules :

1. Manuscripts should be typed in double spacing and submitted in duplicate. Two copies of all figures should be included, one for the printers and one for the referee.

2. References are indicated by superscript numbers in the order in which they appear in the text, and have the following form :

¹ Sargent, W. L. W., and Searle, L., *Astrophys. J. Lett.*, **162**, L155 (1970).

² Fraenkel-Conrat, H., in *Comprehensive Biochemistry* (edit. by Florkin, M., and Stotz, E. H.), **7**, 75 (Elsevier, Amsterdam, 1963).

"Unpublished work", "Private communication" and "Work in preparation" should not be cited as references but may be incorporated in the text. Each reference number should refer to an individual work which has either been published or is in the press.

3. Although the text of longer articles is usually interrupted by headings at suitable intervals, these should be short and informative and not merely "Introduction", "Results", or "Conclusion".

4. Units should either conform to the SI system or be spelled out in full.

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and A. E. Drake. Pp. 23. (London : HMSO, 1970.) 4s (20p) net. [2112]

The Mathilda and Terence Kennedy Institute of Rheumatology. Third Annual Report 1969. Pp. 53. (London : The Mathilda and Terence Kennedy Institute of Rheumatology, 1970.) [2112]

Political and Economic Planning. Broad-sheet 523 : Changing Manpower Needs : a Study of Industrial Training Boards. By Santosh Mukherjee. Pp. iv + 123. (London : PEP, 1970.) 24s. [2212]

Forestry Commission. Report on Forest Research for the year ended March 1970. Pp. vii + 240. (London : HMSO, 1970.) 30s net. [2212]

Ministry of Technology. National Engineering Laboratory—Progress Report 1968/1970. Pp. 20. (East Kilbride, Glasgow : National Engineering Laboratory, 1970.) *gratis*. [2312]

Ministry of Technology : National Physical Laboratory. Electric Units and Standards. By P. Vigoureux. Pp. 31. (London : HMSO, 1970.) 6s (30p) net. [3012]

Smoking and Health Now—a Report of the Royal College of Physicians. Pp. 148. (London : Royal College of Physicians, 1971.) 10s net. [3012]

Royal Greenwich Observatory. Greenwich Time Report. Time and Latitude Service, 1970 January–March. Pp. 125–136. (London : Science Research Council, 1970.) [3012]

Off Sick. Pp. 24. (London : Office of Health Economics, 1971.) 15p. [3112]

Philosophical Transactions of the Royal Society of London. A : Mathematical and Physical Sciences. Vol. 268, No. 1191 (24 December 1970) : A Nonlinear Stability Analysis of the Freezing of a Dilute Binary Alloy. By D. J. Woolkind and L. A. Segel. Pp. 351–380. (London : The Royal Society, 1970.) 16s ; \$0.80. [3112]

Royal Society. Scientific Research in Schools Committee—Report to Council 1970. Pp. 18. (London : The Royal Society, 1970.) [3112]

International Journal of Environmental Studies, Vol. 1, No. 1, October 1970. Edited by J. Rose. Pp. 1–86. Subscription rates (each volume consists of four issues). In Great Britain : Individuals who warrant the journal as for their own personal use, and order direct from the publisher, per volume, postpaid £5 10s. Libraries, research institutions and others, per volume, postpaid £15 10s (London and New York : Gordon and Breach Science Publishers, 1970.) [11]

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